FILE HISTORY

15/231,687

INVENTORS:	Gregory Porreca Uri Laserson
TITLE:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
APPLICATION NO:	15/231,687
FILED:	08 AUG 2016
COMPILED:	21 AUG 2024

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15231687	PORRECA ET AL.
	Examiner	Art Unit
	STEVEN POHNERT	1634

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
consultedJoe Woitach on 112 and art	5/30/2017	SCP
consulted Katherine Salmon on art	5/30/2017	SCP
consulted Ben Blumel on ODP	5/30/2017	SCP
searched EAST	5/30/2017	SCP
inventor search EAST and PALM	5/30/2017	SCP
Assignee search: EAST	5/30/2017	SCP

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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consultedJoe Woitach on 112 and art	5/30/2017	SCP
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Assignee search: EAST	5/30/2017	SCP
consulted Katherine Salmon on art and response	10/21/2017	SCP
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Assignee search: EAST	5/30/2017	SCP
consulted Katherine Salmon on art and response	10/21/2017	SCP
searched EAST	10/23/2017	SCP
inventor search EAST and PALM	10/23/2017	SCP
Assignee search: EAST	10/23/2017	SCP
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Assignee search: EAST	10/04/2018	SCP

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

Petitioner Illumina, Inc., EX1003, p. 5

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/231,687	Porreca et al.
	Examiner	Art Unit
	STEVEN C POHNERT PhD	1634

CPC - Searched*		
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CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
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	15/231,687	Porreca et al.
	Examiner	Art Unit
	STEVEN C POHNERT PhD	1634

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consultedJoe Woitach on 112 and art	5/30/2017	SCP
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inventor search EAST and PALM	10/04/2018	SCP
Assignee search: EAST	10/04/2018	SCP
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consulted Katherine Salmon on claim interpretation, arguments, and art	07/10/2019	SCP
searched EAST	07/10/2019	SCP
inventor search EAST and PALM	07/10/2019	SCP
Assignee search: EAST	07/10/2019	SCP
google search unique tag, unique barcode, unique adapter, amplifying, sequencing	07/10/2019	SCP

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

Petitioner Illumina, Inc., EX1003, p. 7

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/231,687	Porreca et al.
	Examiner	Art Unit
	STEVEN C POHNERT PhD	1634

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
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Search Notes		
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Assignee search: EAST	07/10/2019	SCP
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consulted Katherine Salmon on claim interpretation, arguments, and art	12/17/2019	SCP
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google search unique tag, unique barcode, unique adapter, amplifying, sequencing	12/17/2019	SCP

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Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Petitioner Illumina, Inc., EX1003, p. 10

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/231,687	Porreca et al.
	Examiner	Art Unit
	STEVEN C POHNERT PhD	1634

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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Search Notes		
Search Notes	Date	Examiner
consultedJoe Woitach on 112 and art	5/30/2017	SCP
consulted Katherine Salmon on art	5/30/2017	SCP
consulted Ben Blumel on ODP	5/30/2017	SCP
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Assignee search: EAST	10/23/2017	SCP
consulted Joe Woitach on arguments and art	10/03/2018	SCP

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	Examiner	Art Unit
	STEVEN C POHNERT PhD	1634

searched EAST	10/04/2018	SCP
inventor search EAST and PALM	10/04/2018	SCP
Assignee search: EAST	10/04/2018	SCP
consulted Kevin Orwig on claim interpretation, arguments, and art	07/10/2019	SCP
consulted Katherine Salmon on claim interpretation, arguments, and art	07/10/2019	SCP
searched EAST	07/10/2019	SCP
inventor search EAST and PALM	07/10/2019	SCP
Assignee search: EAST	07/10/2019	SCP
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Assignee search: EAST	12/17/2019	SCP
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consulted Katherine Salmon on 112, declaration and art	07/08/2020	SCP
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Assignee search: EAST	07/09/2020	SCP
google search unique tag, unique barcode, unique adapter, amplifying, sequencing	07/09/2020	SCP

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

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	15/231,687	Porreca et al.
	Examiner	Art Unit
	STEVEN C POHNERT PhD	1634

Petitioner Illumina, Inc., EX1003, p. 13

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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L2	31	(("PORRECA") near3 ("Gregory")).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/10/23 08:27
L3	2	(("LASERSON") near3 ("Uri")).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2017/10/23 08:27
L4	68	(good near2 start near2 genetics).as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/10/23 08:28
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L6	8	(l1 or l2 or l3 or l4) and (unique near2 differentiator near2 tag)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2017/10/23 08:29
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EAST Search History

EAST Search History (Prior Art)

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L2	72	(good near2 start near2 genetics).as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/10/04 10:53
L3	20	(("LASERSON") near3 ("Uri")).INV.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/10/04 10:53
L4	7	("l12" or l2 or l3) and (differentiator near2 tag)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2018/10/04 10:54
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L7	351	L6 same (amplif$6 or pcr)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/07/10 13:59
L8	74	L7 and @pd< "20080430"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/07/10 13:59
L9	11	L8 and (sequencing near2 errors)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/07/10 13:59
L10	45	((("PORRECA") near3 ("Gregory")) OR (("LASERSON") near3 ("Uri"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2019/07/10 14:05
L11	76	(good near2 start near2 genetics).as. or (molecular near2 loop near2 biosolutions).as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/07/10 14:07
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S4	2563	unique near2 (adapter)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/07/10 11:14
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EAST Search History (Interference)

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EAST Search History

EAST Search History (Prior Art)

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L8	0	(random near2 locus near2 independent)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 10:13

EAST Search History (Interference)

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12/ 17/ 2019 10:14:01 AM
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Google unique tag, unique barcode, unique adapter, amplifying, sequencing

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About 341,000 results (0.62 seconds)

NGS adapters with molecular barcodes | IDT

https://www.idtdna.com › pages › products › next-generation-sequencing

Next generation sequencing adapters with molecular barcodes available from IDT. ... and Wash Kit · Human Cot DNA · xGen Library Amplification Primer Mix ... These adapters contain Illumina's unique dual indexes (UDIs), which mitigate sample ... quantification, since PCR duplicates will share the same insert and UMI tag.

Molecular Biology - Page 251 - Google Books Result

https://books.google.com › books

David P. Clark, Nanette J. Pazdernik, Michelle R. McGehee - 2018 - Science

The reaction is able to fragment the DNA and add the adapters in one single step. ... This step can add a unique tag or index sequence (also called a barcode ... The amplification step is sometimes omitted for NGS libraries that have a lot of ...

Unique barcodes for each molecule for PCR bias elimination

https://genxpro.net › truequant

Unique molecular identifiers, molecular barcodes for PCR bias elimination and ... prior to their amplification, such that each molecule consists of a unique sequence. This is achieved by incorporating a poly-N nucleotide (the TrueQuant Adapter or ... such as smallRNAs, ChIP-Seq tags, Aptamers, RAD-Seq tags or GBS-tags.

Unique, dual-indexed sequencing adapters with UMIs ...

https://bmcgenomics.biomedcentral.com › articles

by LE MacConaill - 2018 - Cited by 53 - Related articles

Jan 8, 2018 - Index sequences can be constructed so that they are less prone to errors ... a UMI appended to the 3' end of the i7 index for molecule barcoding (Fig. 1). ... that are used to tag each DNA library molecule prior to library amplification. ... Unique dual-matched UMI adapters are compatible with shear ligation ...

Tag Sequencing Barcode Set 1-24 - Thermo Fisher Scientific

https://www.thermofisher.com › order › catalog › product

The Tag Sequencing Barcode Set 1-24 provides a set of 24 unique barcode adapters specifically designed for optimal performance in Oncomine cfDNA assays.

Images for unique tag, unique barcode, unique adapter, amplifying, sequencing

→ More images for unique tag, unique barcode, unique adapter, amplifyi... Report images

[PDF] The Use of Molecular Barcodes in Anchored ... - Illumina

https://www.illumina.com › dam › archerdx-molecular-barcode-whitepaper

are labeled with the same sequence tag, and the result- ing library is ... that each molecule in a sample is labeled with a unique sequence prior to PCR amplification. With each ... This adapter contains a sample-specific index of pre-defined ...

Advances in Intranuclear Space Research and Application: ...

https://books.google.com › books

2013 - Science

in one embodiment, the at least one **sequence** is **adaptor sequence** that ... one known **sequence** can also include a **unique tag**, such as a **barcode sequence**. ... nucleic acids can be **amplified** such that nucleic acids with known **sequences** on ...

Importance of Root Symbiomes for Plant Nutrition: New ...

https://books.google.com › books

Kevin Garcia, Heike Bücking, Sabine Dagmar Zimmermann - 2020

Wells of different colors depict **distinct barcode sequences**. ... a single mRNA molecule followed by terminal **tagging** to add the 5 **adapter** is depicted on the right. ... If **amplification** is desired, random hexamer primers can be used in the RT step ...

Handbook of Maize: Genetics and Genomics

https://books.google.com › books

Jeff L. Bennetzen, Sarah C. Hake - 2009 - Technology & Engineering

For example, identifying individuals in "2-D pools" by a **unique** row and column ... Using available 96-well liquid handling, two genes at a time can be **amplified** ... short "**barcode sequence tags**" **unique** to each pool to associate a **unique** row and ... The two **adapters** required for whatever **sequencing** platform is being used ...

Searches related to unique tag, unique barcode, unique adapter, amplifying, sequencing

index hopping	**illumina adapters explained**
idt unique **dual indexes**	**umi adapters**
unique **molecular identifiers**	**idt umi adapters**
illumina adapter **sequences**	**illumina dual index adapters**

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	54	((("PORRECA") near3 ("Gregory")) OR (("LASERSON") near3 ("Uri"))).INV.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2020/07/09 16:24
L2	83	(good near2 start near2 genetics).as. or (molecular near2 loop near2 biosolutions).as.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2020/07/09 16:25
L3	321	(unique near2 tag$3 near2 target)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2020/07/09 16:26
L4	209	l3 and amplif$6 and sequenc$5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2020/07/09 16:26
L5	62	l3 same amplif$6 same sequenc$5	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2020/07/09 16:26
L6	0	(l1 or l2) and l4	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2020/07/09 16:27
L7	359	(unique$3 near2 tag$3 near2 target)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2020/07/09 16:27
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			JPO; DERWENT; IBM_TDB			
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S2	3	"20060008824".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2020/07/08 10:51
S3	3	"20080090239".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2020/07/08 17:21

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EAST Search History

EAST Search History (Prior Art)

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L4	48	(L1 OR L2) AND MICROVESICLE.CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 14:32
L5	34	L4 AND (BLOOD OR URINE OR PLASMA OR SERUM).CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 14:33
L6	4	L5 AND ((BRAIN NEAR2 CANCER) OR GLIOMA).CLM.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 14:34
S6	4	14/924245	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 10:28
S7	0	S6 and (administering near2 brain near2 tumor near2 treatment)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 10:28
S8	0	S6 and (administer$4 near2 brain near2 tumor near2 treatment)	US-PGPUB; USPAT; USOCR; FPRS;	OR	ON	2019/12/17 10:28

			EPO; JPO; DERWENT; IBM_TDB			
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S12	4	S6 and (treatment)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 10:29
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S14	4	S6 and ((brain near2 tumor) with treat$4)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 10:45
S15	4	S6 and ("0.22")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2019/12/17 10:52

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Electronic Acknowledgement Receipt	
EFS ID:	26572491
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Matthew York
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	08-AUG-2016
Filing Date:	
Time Stamp:	21:04:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2800
RAM confirmation Number	7051
Deposit Account	500369
Authorized User	YORK, MATTHEW P.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		GSGE-002-04US_Preliminary_Amendment.pdf	29528 d85bec218cb38a2c6121495ab5b3117272dedea5	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Specification	2	2
	Claims	3	4
	Applicant Arguments/Remarks Made in an Amendment	5	5

Warnings:

Information:

2	TrackOne Request	GSGE-002_04US_Request_Prioritized_Exam.pdf	114206 cf1545318e7174a4f6e85c99b89d4548e2befa3f	no	2

Warnings:

Information:

3		GSGE-002-04US_Application.pdf	4858997 fdbc9b0e39764da43e7e30008e9539a4a0f3ac5b	yes	99

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	88
	Claims	89	98
	Abstract	99	99

Warnings:

Information:					
4	Drawings-only black and white line drawings	GSGE-002-04US_Figures.pdf	251734 f86054612efc395a20668e8e9a7474887c69d4f3	no	16
Warnings:					
Information:					
5	Application Data Sheet	GSGE-002-04US_ADS.pdf	1823102 40982a40a7d66ae38cb068c63e3fba2dfb9396b0	no	9
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	38959 52e1e875711c3a9b3d033c4f56dd40b5f49f9a3b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	7116526		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	NOT YET ASSIGNED
SERIAL NUMBER:	NOT YET ASSIGNED	CONF. NO.:	NOT YET ASSIGNED
FILING DATE:	NOT YET ASSIGNED	EXAMINER:	NOT YET ASSIGNED
RELATED CASE:	Continuation of 13/266,862, filed March 13, 2012		
TITLE:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Please enter the following amendments to the specification and claims with the entry of the accompanying continuation application.

Applicant believes that no additional fees are due with respect to this Preliminary Amendment.

Amendments to the Specification begin on page 2.

Amendments to the Claims begin on page 3.

Remarks begin on page 5.

Amendments to the Specification:

Please amend the "Related Applications" section at page 1 of the as-filed specification as follows:

RELATED APPLICATIONS

This application is a continuation of U.S. Application No. 13/266,862, filed March 13, 2012, which is a national phase application that claims the benefit of, and priority to, international PCT Application No. PCT/US2010/001293, filed April 30, 2010, which claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. ~~provisional application serial number~~ 61/174,470, filed April 30, 2009, U.S. Provisional Application No. ~~provisional application serial number~~ 61/178,923, filed May 15, 2009, U.S. Provisional Application No. ~~provisional application serial number~~ 61/179,358, filed May 18, 2009, and U.S. Provisional Application No. ~~provisional application serial number~~ 61/182,089, filed May 28, 2009, the entire contents of each of which are incorporated herein by reference.

Amendments to the Claims:

Please cancel claims 1-67 and add new claims 68-78. This listing of claims replaces all prior versions and listings of claims in the application.

1-67. (Canceled)

68. (New) A method for nucleic acid identification, the method comprising the steps of:

applying a unique differentiator tag to each member of a plurality of nucleic acid molecules obtained from a biological sample;

amplifying said nucleic acid molecules;

sequencing amplicons obtained in said amplifying step; and

identifying a sequence for said nucleic acid molecules.

69. (New) The method of claim 68, wherein said identifying step comprises identifying said unique differentiator tags.

70. (New) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon the number of said unique differentiator tags.

71. (New) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

72. (New) The method of claim 71, wherein said common identifier is used to identify a sample source.

73. (New) The method of claim 72, wherein said common identifier is used to identify a patient.

Petitioner Illumina, Inc., EX1003, p. 33

74. (New) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (New) The method of claim 68, wherein said plurality of nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (New) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

77. (New) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

78. (New) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

Petitioner Illumina, Inc., EX1003, p. 34

Remarks

Applicant submits herewith a continuation application of parent U.S. Patent Application No. 13/266,862, filed March 13, 2012. Applicant submits amendments to the specification, specifically to amend the "Related Applications" section to reflect that the instant filed application is a continuation of U.S. Patent Application No. 13/266,862 and to further reflect that the parent application is a national phase application and claims the benefit of and priority to PCT/US2010/001293, filed April 30, 2010. Applicant also submits new claims and cancelations, by which claims 1-67 are canceled and new claims 68-78 are added. Support for new claims 68-78 can be found in the original claims and specification as-filed, at least on page 2 lines 21-25, page 3 lines 1-6, page 4 lines 8-11, page 5 lines 4-6 and 12-14, page 6 line 13 to page 7 line 10, page 9 lines 7-26, page 29 lines 18-32, page 38 lines 4-19, page 39 lines 16-20, and page 40 lines 4-20, . No new matter has been introduced via new claims 68-78.

Summary

If there are any questions regarding these remarks, the Office is invited and encouraged to contact Applicant's undersigned representative.

Dated: August 8, 2016

Respectfully submitted,
BROWN RUDNICK LLP

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Boston, MA 02111
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/Thomas C. Meyers/
Thomas C. Meyers Reg. No. 36,989
Attorney for Applicant
Email: tmeyers@brownrudnick.com

62533044-029258/0078

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Gregory Porreca	Nonprovisional Application Number (if known):	
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Thomas C. Meyers/	Date August 8, 2016
Name (Print/Typed) Thomas C. Meyers	Practitioner Registration Number 36,989

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119(e) of U.S. provisional application serial number 61/174,470, filed April 30, 2009, U.S. provisional application serial number 61/178,923, filed May 15, 2009, U.S. provisional application serial number 61/179,358, filed May 18, 2009, and U.S. provisional application serial number 61/182,089, filed May 28, 2009, the entire contents of each of which are incorporated herein by reference.

FIELD OF INVENTION

The invention relates to methods and compositions for determining genotypes in patient samples.

BACKGROUND OF THE INVENTION

Information about the genotype of a subject is becoming more important and relevant for a range of healthcare decisions as the genetic basis for many diseases, disorders, and physiological characteristics is further elucidated. Medical advice is increasingly personalized, with individual decisions and recommendations being based on specific genetic information. Information about the type and number of alleles at one or more genetic loci impacts disease risk, prognosis, therapeutic options, and genetic counseling amongst other healthcare considerations.

For cost-effective and reliable medical and reproductive counseling on a large scale, it is important to be able correctly and unambiguously identify the allelic status for many different genetic loci in many subjects.

Numerous technologies have been developed for detecting and analyzing nucleic acid sequences from biological samples. These technologies can be used to genotype subjects and determine the allelic status of any locus of interest. However, they are not sufficiently robust and cost-effective to be scaled up for reliable high throughput analysis of many genetic loci in large numbers of patients. The frequency of incorrect or ambiguous calls is too high for current technology to manage large numbers of patient

samples without involving expensive and time-consuming steps to resolve uncertainties and provide confidence in the information output.

SUMMARY OF THE INVENTION

Aspects of the invention relate to preparative and analytical methods and compositions for evaluating genotypes, and in particular, for determining the allelic identity (or identities in a diploid organism) of one or more genetic loci in a subject.

Aspects of the invention are based, in part, on the identification of different sources of ambiguity and error in genetic analyses, and, in part, on the identification of one or more approaches to avoid, reduce, recognize, and/or resolve these errors and ambiguities at different stages in a genetic analysis.

According to aspects of the invention, certain types of genetic information can be under-represented or over-represented in a genetic analysis due to a combination of stochastic variation and systematic bias in any of the preparative stages (e.g., capture, amplification, etc.), determining stages (e.g., allele-specific detection, sequencing, etc.), data interpretation stages (e.g., determining whether the assay information is sufficient to identify a subject as homozygous or heterozygous), and/or other stages.

According to aspects of the invention, error or ambiguity may be apparent in a genetic analysis, but not readily resolved without running additional samples or more expensive assays (*e.g.*, array-based assays may report no-calls due to noisy/low signal). According to further aspects of the invention, error or ambiguity may not be accounted for in a genetic analysis and incorrect base calls may be made even when the evidence for them is limited and/or not statistically significant (*e.g.*, next-generation sequencing technologies may report base calls even if the evidence for them is not statistically significant). According to further aspects of the invention error or ambiguity may be problematic for a multi-step genetic analysis because it is apparent but not readily resolved in one or more steps of the analysis and not apparent or accounted for in other steps of the analysis.

In some embodiments, sources of error and ambiguity in one or more steps can be addressed by capturing and/or interrogating each target locus of interest with one or more sets of overlapping probes that are designed to overcome any systematic bias or stochastic effects that may impact the complexity and/or fidelity of the genetic information that is generated.

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In some embodiments, sources of error and ambiguity in one or more steps can be addressed by capturing and/or interrogating each target locus of interest with at least one set of probes, wherein different probes are labeled with different identifiers that can be used to track the assay reactions and determine whether certain types of genetic information are under-represented or over-represented in the information that is generated.

In some embodiments, errors and ambiguities associated with the analysis of regions containing large numbers of sequence repeats are addressed by systematically analyzing frequencies of certain nucleic acids at particular stages in an assay (e.g., at a capture, sequencing, or detection stage). It should be appreciated that such techniques may be particularly useful in the context of a standardized protocol that is designed to allow many different loci to be evaluated in parallel without requiring different assay procedures for each locus. In some embodiments, the use of a single detection modality (*e.g.*, sequencing) to assay multiple types of genetic lesions (*e.g.*, point mutations, insertions/deletions, length polymorphisms) is advantageous in the clinical setting. In some embodiments of the invention, methods are provided that facilitate the use of multiple sample preparation steps in parallel, coupled with multiple analytical processes following sequence detection. Thus, in some embodiments of the invention, an improved workflow is provided that reduces error and uncertainty when simultaneously assaying different types of genetic lesions across multiple loci in multiple patients.

In some embodiments, aspects of the invention provide methods for overcoming preparative and/or analytical bias by combining two or more techniques, each having a different bias (e.g., a known bias towards under-representation or over-representation of one or more types of sequences), and using the resulting data to determine a genetic call for a subject with greater confidence.

It should be appreciated that in some embodiments, aspects of the invention relate to multiplex diagnostic methods. In some embodiments, multiplex diagnostic methods comprise capturing a plurality of genetic loci in parallel (e.g., one or more genetic loci from Table 1). In some embodiments, the genetic loci possess one or more polymorphisms (e.g., one or more polymorphisms from Table 2) the genotypes of which correspond to disease causing alleles. Accordingly, in some embodiments, the disclosure provides methods for assessing multiple heritable disorders in parallel. In some

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embodiments, methods are provided for diagnosing multiple heritable disorders in parallel at a pre-implantation, prenatal, perinatal, or postnatal stage. In some embodiments, the disclosure provides methods for analyzing multiple genetic loci (e.g., a plurality of target nucleic acids selected from Table 1) from a patient sample, such as a blood, pre-implantation embryo, chorionic villus or amniotic fluid sample, or other sample (e.g., other biological fluid or tissue sample such as a biopsy sample) as aspects of the invention are not limited in this respect.

Other samples may include tumor tissue or circulating tumor cells. In some embodiments, a patient sample (*e.g.*, a tumor tissue or cell sample) is mosaic for one or more mutations of interest, and thus, may require higher sensitivity than is needed for a germline mutation analysis. In some embodiments, a sample comprises cells from a non-host organism (*e.g.*, bacterial or viral infections in a human subject) or a sample for environmental monitoring (*e.g.*, bacterial, viral, fungal composition of a soil, water, or air sample).

Accordingly, in some embodiments, aspects of the methods disclosed herein relate to genotyping a polymorphism of a target nucleic acid. In some embodiments, the genotyping may comprise determining that one or more alleles of the target nucleic acid are heterozygous or homozygous. In further embodiments, the genotyping may comprise determining the sequence of a polymorphism and comparing that sequence to a control sequence that is indicative of a disease risk. In some embodiments, the polymorphism is selected from a locus in Table 1 or Table 2. However, it should be appreciated that any locus associated with a disease or condition of interest may be used.

In some embodiments, a diagnosis, prognosis, or disease risk assessment is provided to a subject based on a genotype determined for that subject at one or more genetic loci (e.g., based on the analysis of a biological sample obtained from that subject). In some embodiments, an assessment is provided to a couple, based on their respective genotypes at one or more genetic loci, of the risk of their having one or more children having a genotype associated with a disease or condition (e.g., a homozygous or heterozygous genotype associated with a disease or condition). In some embodiments, a subject or a couple may seek genetic or reproductive counseling in connection with a genotype determined according to embodiments of the invention. In some embodiments, genetic information from a tumor or circulating tumor cells is used to determine prognosis and guide selection of appropriate drugs/treatments.

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It should be appreciated that any of the methods or compositions described herein may be used in combination with any of the medical evaluations associated with one or more genetic loci as described herein.

In some embodiments, aspects of the invention provide effective methods for overcoming challenges associated with systematic errors (bias) and/or stochastic effects in multiplex genomic capture and/or analysis (including sequencing analysis). In some embodiments, aspects of the invention are useful to avoid, reduce and/or account for variability in one or more sampling and/or analytical steps. For example, in some embodiments, variability in target nucleic acid representation and unequal sampling of heterozygous alleles in pools of captured target nucleic acids can be overcome.

Accordingly, in some embodiments, the disclosure provides methods that reduce variability in the detection of target nucleic acids in multiplex capture methods. In other embodiments, methods improve allelic representation in a capture pool and, thus, improve variant detection outcomes. In certain embodiments, the disclosure provides preparative methods for capturing target nucleic acids (e.g., genetic loci) that involve the use of different sets of multiple probes (e.g., molecular inversion probes MIPs) that capture overlapping regions of a target nucleic acid to achieve a more uniform representation of the target nucleic acids in a capture pool compared with methods of the prior art. In other embodiments, methods reduce bias, or the risk of bias, associated with large scale parallel capture of genetic loci, e.g., for diagnostic purposes. In other embodiments, methods are provided for increasing reproducibility (e.g., by reducing the effect of polymorphisms on target nucleic acid capture) in the detection of a plurality of genetic loci in parallel. In further embodiments, methods are provided for reducing the effect of probe synthesis and/or probe amplification variability on the analysis of a plurality of genetic loci in parallel.

According to some aspects, methods of analyzing a plurality of genetic loci are provided. In some embodiments, the methods comprise contacting each of a plurality of target nucleic acids with a probe set, wherein each probe set comprises a plurality of different probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids flanking the same strand of one of a plurality of subregions of the target nucleic acid, wherein the subregions of the target nucleic acid are different, and wherein each subregion overlaps with at least one other subregion, isolating a plurality of nucleic acids each having a nucleic acid sequence of a different

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subregion for each of the plurality of target nucleic acids, and analyzing the isolated nucleic acids.

In other embodiments, methods comprise contacting each of a plurality of target nucleic acids with a probe set, wherein each probe set comprises a plurality of different probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids flanking the same strand of one of a plurality of subregions of the target nucleic acid, wherein the subregions of the target nucleic acid are different, and wherein a portion of the 5' region and a portion of the 3' region of a probe have, respectively, the sequence of the 5' region and the sequence of the 3' region of a different probe, isolating a plurality of nucleic acids each having a nucleic acid sequence of a different subregion for each of the plurality of target nucleic acids, and analyzing the isolated nucleic acids.

Aspects of the disclosure are based, in part, on the discovery of methods for overcoming problems associated with systematic and random errors (bias) in genome capture, amplification and sequencing methods, namely high variability in the capture and amplification of nucleic acids and disproportionate representation of heterozygous alleles in sequencing libraries. Accordingly, in some embodiments, the disclosure provides methods that reduce errors associated with the variability in the capture and amplification of nucleic acids. In other embodiments, the methods improve allelic representation in sequencing libraries and, thus, improve variant detection outcomes. In certain embodiments, the disclosure provides preparative methods for capturing target nucleic acids (e.g., genetic loci) that involve the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules. In some embodiments, the differentiator tag sequence permit the detection of bias based on the occurrence of combinations of differentiator tag and target sequences observed in a sequencing reaction. In other embodiments, the methods reduce errors caused by bias, or the risk of bias, associated with the capture, amplification and sequencing of genetic loci, e.g., for diagnostic purposes.

Aspects of the invention relate to providing sequence tags (referred to as differentiator tags) that are useful to determine whether target nucleic acid sequences identified in an assay are from independently isolated target nucleic acids or from multiple copies of the same target nucleic acid molecule (e.g., due to bias in a preparative step, for example, amplification). This information can be used to help analyze a

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threshold number of independently isolated target nucleic acids from a biological sample in order to obtain sequence information that is reliable and can be used to make a genotype conclusion (e.g., call) with a desired degree of confidence. This information also can be used to detect bias in one or more nucleic acid preparative steps.

In some embodiments, the methods disclosed herein are useful for any application where reduction of bias, e.g., associated with genomic isolation, amplification, sequencing, is important. For example, detection of cancer mutations in a heterogeneous tissue sample, detection of mutations in maternally-circulating fetal DNA, and detection of mutations in cells isolated during a preimplantation genetic diagnostic procedure.

Accordingly, in some aspects, methods of genotyping a subject are provided. In some embodiments, the methods comprise determining the sequence of at least a threshold number of independently isolated nucleic acids, wherein the sequence of each isolated nucleic acid comprises a target nucleic acid sequence and a differentiator tag sequence, wherein the threshold number is a number of unique combinations of target nucleic acid and differentiator tag sequences, wherein the isolated nucleic acids are identified as independently isolated if they comprise unique combinations of target nucleic acid and differentiator tag sequences, and wherein the target nucleic acid sequence is the sequence of a genomic locus of a subject.

In some embodiments, the isolated nucleic acids are products of a circularization selection-based preparative method, e.g., molecular inversion probe capture products. In other embodiments, the isolated nucleic acids are products of an amplification-based preparative methods. In other embodiments, the isolated nucleic acids are products of hybridization-based preparative methods.

Circularization selection-based preparative methods selectively convert regions of interest (target nucleic acids) into a covalently-closed circular molecule which is then isolated typically by removal (usually enzymatic, e.g. with exonuclease) of any non-circularized linear nucleic acid. Oligonucleotide probes (e.g., molecular inversion probes) are designed which have ends that flank the region of interest (target nucleic acid) and, optionally, primer sites, e.g., sequencing primer sites. The probes are allowed to hybridize to the genomic target, and enzymes are used to first (optionally) fill in any gap between probe ends and second ligate the probe closed. Following circularization, any remaining (non-target) linear nucleic acid is typically removed, resulting in isolation

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(capture) of target nucleic acid. Circularization selection-based preparative methods include molecular inversion probe capture reactions and 'selector' capture reactions. In some embodiments, molecular inversion probe capture of a target nucleic acid is indicative of the presence of a polymorphism in the target nucleic acid.

In amplification-based (e.g., PCR-based or LCR-based, etc.) preparative methods, genomic loci (target nucleic acids) are isolated directly by means of a polymerase chain reaction or ligase chain reaction (or other amplification method) that selectively amplifies each locus using one or more oligonucleotide primers. It is to be understood that primers will be sufficiently complementary to the target sequence to hybridize with and prime amplification of the target nucleic acid. Any one of a variety of art known methods may be utilized for primer design and synthesis. One or more of the primers may be perfectly complementary to the target sequence. Degenerate primers may also be used. Primers may also include additional nucleic acids that are not complementary to target sequences but that facilitate downstream applications, including for example restriction sites and differentiator tag sequences. Amplification-based methods include amplification of a single target nucleic acid and multiplex amplification (amplification of multiple target nucleic acids in parallel).

Hybridization-based preparative methods involve selectively immobilizing target nucleic acids for further manipulation. It is to be understood that one or more oligonucleotides (immobilization oligonucleotides), which comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it. In some embodiments, immobilization oligonucleotides, are either immobilized before hybridization is performed (e.g., Roche/Nimblegen 'sequence capture'), or are prepared such that they include a moiety (e.g. biotin) which can be used to selectively immobilize the target nucleic acid after hybridization by binding to e.g., streptavidin-coated microbeads (e.g. Agilent 'SureSelect').

It should be appreciated that any of the circularization, amplification, and/or hybridization based methods described herein may be used in connection with one or more of the tiling/staggering, tagging, size-detection, and/or sensitivity enhancing algorithms described herein.

In some embodiments, the methods disclosed herein comprise determining the sequence of molecular inversion probe capture products, each comprising a molecular

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inversion probe and a target nucleic acid, wherein the sequence of the molecular inversion probe comprises a differentiator tag sequence and, optionally, a primer sequence, and wherein the target nucleic acid is a captured genomic locus of a subject, and genotyping the subject at the captured genomic locus based on the sequence of at least a threshold number of unique combinations of target nucleic acid and differentiator tag sequences of molecular inversion probe capture products.

In some embodiments, the methods disclosed herein comprise obtaining molecular inversion probe capture products, each comprising a molecular inversion probe and a target nucleic acid, wherein the sequence of the molecular inversion probe comprises a differentiator tag sequence and, optionally, a primer sequence, wherein the target nucleic acid is a captured genomic locus of the subject, amplifying the molecular inversion probe capture products, and genotyping the subject by determining, for each target nucleic acid, the sequence of at least a threshold number of unique combinations of target nucleic acid and differentiator tag sequence of molecular inversion probe capture products. In certain embodiments, obtaining comprises capturing target nucleic acids from a genomic sample of the subject with molecular inversion probes, each comprising a unique differentiator tag sequence. In specific embodiments, capturing is performed under conditions wherein the likelihood of obtaining two or more molecular inversion probe capture products with identical combinations of target and differentiator tag sequences is equal to or less than a predetermined value, optionally wherein the predetermined value is about 0.05.

In one embodiment, the threshold number for a specific target nucleic acid sequence is selected based on a desired statistical confidence for the genotype. In some embodiments, the methods further comprising determining a statistical confidence for the genotype based on the number of unique combinations of target nucleic acid and differentiator tag sequences.

According to some aspects, methods of analyzing a plurality of genetic loci are provided. In some embodiments, the methods comprise obtaining a plurality of molecular inversion probe capture products each comprising a molecular inversion probe and a target nucleic acid, wherein the sequence of the molecular inversion probe comprises a differentiator tag sequence and, optionally, a primer sequence (e.g., a sequence that is complementary to the sequence of a nucleic acid that is used as a primer for sequencing or other extension reaction), amplifying the plurality of molecular

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inversion probe capture products, determining numbers of occurrence of combinations of target nucleic acid and differentiator tag sequence of molecular inversion probe capture products in the amplified plurality, and if the number of occurrence of a specific combination of target nucleic acid sequence and differentiator tag sequence exceeds a predetermined value, detecting bias in the amplification of the molecular inversion probe comprising the specific combination. In some embodiments, the methods further comprise genotyping target sequences in the plurality, wherein the genotyping comprises correcting for bias, if detected.

In some embodiments, the target nucleic acid is a gene (or portion thereof) selected from Table 1. In some embodiments, the genotyping comprises determining the sequence of a target nucleic acid (e.g., a polymorphic sequence) at one or more (both) alleles of a genome (a diploid genome) of a subject. In certain embodiments, the genotyping comprises determining the sequence of a target nucleic acid at both alleles of a diploid genome of a subject, wherein in the target nucleic acid comprises, or consists of, a sequence of Table 1, Table 2, or other locus of interest.

In some embodiments, aspects of the invention provide methods and compositions for identifying nucleic acid insertions or deletions in genomic regions of interest without determining the nucleotide sequences of these regions. Aspects of the invention are particularly useful for detecting nucleic acid insertions or deletions in genomic regions containing nucleic acid sequence repeats (e.g., di- or tri-nucleotide repeats). However, the invention is not limited to analyzing nucleic acid repeats and may be used to detect insertions or deletions in any target nucleic acid of interest. Aspects of the invention are particularly useful for analyzing multiple loci in a multiplex assay.

In some embodiments, aspects of the invention relate to determining whether an amount of target nucleic acid that is captured in a genomic capture assay is higher or lower than expected. In some embodiments, a statistically significant deviation from an expected amount (e.g., higher or lower) is indicative of the presence of a nucleic acid insertion or deletion in the genomic region of interest. In some embodiments, the amount is a number of nucleic acid molecules that are captured. In some embodiments, the amount is a number of independently captured nucleic acid molecules in a sample. It should be appreciated that the captured nucleic acids may be literally captured from a sample, or their sequences may be captured without actually capturing the original nucleic acids in the sample. For example, nucleic acid sequences may be captured in an

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assay that involves a template-based extension of nucleic acids having the region of interest, in the sample.

Aspects of the invention are based on the recognition that the efficiency of certain capture techniques is affected by the length of the nucleic acid being captured. Accordingly, an increase or decrease in the length of a target nucleic acid (e.g., due to an insertion or deletion of a repeated sequence) can alter the capture efficiency of that nucleic acid. In some embodiments, a difference in the capture efficiency (e.g., a statistically significant difference in the capture efficiency) of a target nucleic acid is indicative of an insertion or deletion in the target nucleic acid. It should be appreciated that the capture efficiency for a target nucleic acid may be evaluated based on an amount of captured nucleic acid (e.g., number of captured nucleic acid molecules) relative to a control amount (e.g., based on an amount of control nucleic acid that is captured). However, the invention is not limited in this respect and other techniques for evaluating capture efficiency also may be used.

According to aspects of the invention, evaluating the capture efficiency as opposed to determining the sequence of the entire repeat region reduces errors associated with sequencing through repeat regions. Repeat sequences often give rise to stutters or skips in sequencing reactions that make it very difficult to accurately determine the number of repeats in a target region without running multiple sequencing reactions under different conditions and carefully analyzing the results. Such procedures are cumbersome and not readily scalable in a manner that is consistent with high throughput analyses of target nucleic acids. In some embodiments, repeat regions may be longer than the length of the individual sequence read, making length determination on the basis of a single read impossible. For example, when using next-generation sequencing the repeat regions may be longer than the length of the individual sequence read, making length determination on the basis of a single read impossible. Accordingly, aspects of the invention are useful to increase the sensitivity of detecting insertions or deletions in target regions, particularly target regions containing repeated sequences.

In some embodiments, aspects of the invention relate to capturing genomic nucleic acid sequences using a molecular inversion probe (e.g., MIP or Padlock probe) technique, and determining whether the amount (e.g., number) of captured sequences is higher or lower than expected. In some embodiments, the amount (e.g., number) of captured sequences is compared to an amount (e.g., number) of sequences captured in a

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control assay. The control assay may involve analyzing a control sample that contains a nucleic acid from the same genetic locus having a known sequence length (e.g., a known number of nucleic acid repeats). However, a control may involve analyzing a second (e.g., different) genetic locus that is not expected to contain any insertions or deletions. The second genetic locus may be analyzed in the same sample as the locus being interrogated or in a different sample where its length has been previously determined. The second genetic locus may be a locus that is not characterized by the presence of nucleic acid repeats (and thus not expected to contain insertions or deletions of the repeat sequence).

In some embodiments, a target nucleic acid region that is being evaluated may be determined by the identity of the targeting arms of a probe that is designed to capture the target region (or sequence thereof). For example, the targeting arms of a MIP probe may be designed to be complementary (e.g., sufficiently complementary for selective hybridization and//or polymerase extension and/or ligation) to genomic regions flanking a target region suspected of containing an insertion or deletion. It should be appreciated that two targeting arms may be designed to be complementary (e.g., sufficiently complementary for selective hybridization and/or polymerase extension and/or ligation) to the two flanking regions that are immediately adjacent (e.g., immediately 5' and 3', respectively) to a region of a sequence repeat on one strand of a genomic nucleic acid. However, one or both targeting arms may be designed to hybridize several bases (e.g., 1-5, 5-10, 10-25, 25-50, or more) upstream or downstream from the repeat region in such a way that the captured sequence includes a region of unique genomic sequence that on one or both sides of the repeat region. This unique region can then be used to identify the captured target (e.g., based on sequence or hybridization information).

In some embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) different loci may be interrogated in parallel in a single assay (e.g., in a multiplex assay). In some embodiments, the ratio of captured nucleic acids for each locus may be used to determine whether a nucleic acid insertion or deletion is present in one locus relative to the other. For example, the ratio may be compared to a control ratio that is representative of the two loci when neither one has an insertion or deletion relative to control sequences (e.g., sequences that are normal or known to be associated with healthy phenotypes for those loci). However, the amount of captured nucleic acids may be compared to any suitable control as discussed herein.

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The locus of a captured sequence may be identified by determining a portion of unique sequence 5' and/or 3' to the repeat region in the target nucleic acid suspected of containing a deletion or insertion. This does not require sequencing the captured repeat region itself. However, some or all of the repeat region also could be sequenced as aspects of the invention are not limited in this respect.

Aspects of the invention may be combined with one or more sequence-based assays (e.g., SNP detection assays), for example in a multiplex format, to determine the genotype of one or more regions of a subject.

In some embodiments, methods of detecting a polymorphism in a nucleic acid in a biological sample are provided. In some embodiments, the methods comprise evaluating the efficiency of capture at one or more loci and determining whether one or both alleles at that locus contain an insertion or deletion relative to a control locus (e.g., a locus indicative of a length of repeat sequence that is associated with a healthy phenotype).

Accordingly, aspects of the invention relate to methods for determining whether a target nucleic acid has an abnormal length by evaluating the capture efficiency of a target nucleic acid in a biological sample from a subject, wherein a capture efficiency that is different from a reference capture efficiency is indicative of the presence, in the biological sample, of a target nucleic acid having an abnormal length. It should be appreciated that the term "abnormal" is a relative term based on a comparison to a "normal" length. In some embodiments, a normal length is a length that is associated with a normal (e.g., healthy or non-carrier phenotype). Accordingly, an abnormal length is a length that is either shorter or longer than the normal length. In some embodiments, the presence of an abnormal length is indicative of an increased risk that the locus is associated with a disease or a disease carrier phenotype. In some embodiments, the abnormal length is indicative that the subject is either has a disease or condition or is a carrier of a disease or condition (e.g., associated with the locus). However, it should be appreciated that the description of embodiments relating to detecting the presence of an abnormal length also support detecting the presence of a length that is different from an expected or control length.

In some embodiments, aspects of the invention relate to estimating the length of a target nucleic acid (e.g., of a sub-target region within a target nucleic acid). In some embodiments, aspects of the invention relate to methods for estimating the length of a

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target nucleic acid by contacting the target nucleic acid with a plurality of detection probes under conditions that permit hybridization of the detection probes to the target nucleic acid, wherein each detection probe is a polynucleotide that comprises a first arm that hybridizes to a first region of the target nucleic acid and a second arm that hybridizes to a second region of the target nucleic acid, wherein the first and second regions are on a common strand of the target nucleic acid, and wherein the nucleotide sequence of the target between the 5' end of the first region and the 3' end of the second region is the nucleotide sequence of a sub-target nucleic acid; and capturing a plurality of sub-target nucleic acids that are hybridized with the plurality of detection probes; and measuring the frequency of occurrence of a sub-target nucleic acid in the plurality of sub-target nucleic acids, wherein the frequency of occurrence of the sub-target nucleic acid in the plurality of sub-target nucleic acids is indicative of the length of the sub-target nucleic acid. It should be appreciated that methods for estimating a nucleic acid length may involve comparing a capture efficiency for a target nucleic acid region to two or more reference efficiencies for known nucleic acid lengths in order to determine whether the target nucleic acid region is smaller, intermediate, or larger in size than the known control lengths. In some embodiments, a series of nucleic acids of known different lengths may be used to provide a calibration curve for evaluating the length of a target nucleic acid region of interest.

In some embodiments, the capture efficiency of a target region suspected of having a deletion or insertion is determined by comparing the capture efficiency to a reference indicative of a normal capture efficiency. In some embodiments, the capture efficiency is lower than the reference capture efficiency. In some embodiments, the subject is identified as having an insertion in the target region. In some embodiments, the capture efficiency is higher than the reference capture efficiency. In some embodiments, the subject is identified as having a deletion in the target region. In some embodiments, the subject is identified as being heterozygous for the insertion. In some embodiments, the subject is identified as being heterozygous for the deletion.

In some embodiments of any of the methods described herein (e.g., tiling/staggering, tagging, size-detection, and/or sensitivity enhancement) aspects of the invention relate to capturing a sub-target nucleic acid (or a sequence of a sub-target nucleic acid). In some embodiments, a molecular inversion probe technique is used. In some embodiments, a molecular inversion probe is a single linear strand of nucleic acid

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that comprises a first targeting arm at its 5' end and a second targeting arm at its 3' end, wherein the first targeting arm is capable of specifically hybridizing to a first region flanking one end of the sub-target nucleic acid, and wherein the second targeting arm is capable of specifically hybridizing to a second region flanking the other end of the sub-target nucleic acid on the same strand of the target nucleic acid. In some embodiments, the first and second targeting arms are between about 10 and about 100 nucleotides long. In some embodiments, the first and second targeting arms are about 10-20, 20-30, 30-40, or 40-50 nucleotides long. In some embodiments, the first and second targeting arms are about 20 nucleotides long. In some embodiments, the first and second targeting arms have the same length. In some embodiments, the first and second targeting arms have different lengths. In some embodiments, each pair of first and second targeting arms in a set of probes has the same length. Accordingly, if one of the targeting arms is longer, the other one is correspondingly shorter. This allows for a quality control step in some embodiments to confirm that all captured probe/target sequence products have the same length after a multiplexed plurality of capture reactions. In some embodiments, a set of probes may be designed to have the same length if the intervening region is varied to accommodate any differences in the length of either one or both of the first and second targeting arms.

In some embodiments, the hybridization Tms of the first and second targeting arms are similar. In some embodiments, the hybridization Tms of the first and second targeting arms are within 2-5 °C of each other. In some embodiments, the hybridization Tms of the first and second targeting arms are identical. In some embodiments, the hybridization Tms of the first and second targeting arms are close to empirically-determined optima but not necessarily identical.

In some embodiments, the first and second targeting arms of a molecular inversion probe have different Tms. For example, the Tm of the first targeting arm (at the 5' end of the molecular inversion probe) may be higher than the Tm of the second targeting arm (at the 3' end of the molecular inversion probe). According to aspects of the invention, and without wishing to be bound by theory, a relatively high Tm for the first targeting arm may help avoid or prevent the first targeting arm from being displaced after hybridization by the extension product of the 3' end of the second targeting arm. It should be appreciated that a reference to the Tm of a targeting arm as used herein relates to the Tm of hybridization of the targeting arm to a nucleic acid having the

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complementary sequence (e.g., the region of the target nucleic acid that has a sequence that is complementary to the sequence of the targeting arm). It also should be appreciated that the Tms of the targeting arms described herein may be calculated using any appropriate method. For example, in some embodiments an experimental method (e.g., a gel shift assay, a hybridization assay, a melting curve analysis, for example in a PCR machine with a SYBR dye by stepping through a temperature ramp while monitoring signal level from an intercalating dye, for example, bound to a double-stranded DNA, etc.) may be used to determine one or more Tms empirically. In some embodiments, an optimal Tm may be determined by evaluating the number of products formed (e.g., for each of a plurality of MIP probes), and determining the optimal Tm as the center point in a histogram of Tm for all targeting arms. In some embodiments, a predictive algorithm may be used to determine a Tm theoretically. In some embodiments, a relatively simple predictive algorithm may be used based on the number of G/C and A/T base pairs when the sequence is hybridized to its target and/or the length of the hybridized product (e.g., for example, 64.9 + 41 * ([G+C] - 16.4) / (A + T + G + C), see for example, Wallace,R.B., Shaffer,J., Murphy,R.F., Bonner,J., Hirose,T., and Itakura,K. (1979) Nucleic Acids Res 6:3543-3557). In some embodiments, a more complex algorithm may be used to account for the effects of base stacking entropy and enthalpy, ion concentration, and primer concentration (see, for example, SantaLucia J (1998), Proc Natl Acad Sci USA, 95:1460-5). In some embodiments an algorithm may use modified parameters (e.g., nearest-neighbor parameters for basepair entropy/enthalpy values). It should be appreciated that any suitable algorithm may be used as aspects of the invention are not limited in this respect. However, it also should be appreciated that different methodologies may results in different calculated or predicted Tms for the same sequences. Accordingly, in some embodiments, the same empirical and/or theoretical method is used to determine the Tms of different sequences for a set of probes to avoid a negative impact of any systematic difference in the Tm determination or prediction when designing a set of probes with predetermined similarities or differences for different Tms.

In some embodiments, the Tm of the first targeting arm may be about 1 °C, about 2 °C, about 3 °C, about 4 °C, about 5 °C, or more than about 5 °C higher than the Tm of the second targeting arm. In some embodiments, each probe in a plurality of probes (e.g., each probe in a set of 5-10, each probe in a set of at least 10, each probe in a set of

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10-50, each probe in a set of 50-100, each probe in a set of 100-500, each probe in a set of 500-1,000, each probe in a set of 1,000-1,500, each probe in a set of 1,500-2,000, each probe in a set of 2,000-3,000, 3,000-5,000, 5,000-10,000 or each probe in a set of at least 5,000 different probes) has a unique first targeting arm (e.g., they all have different sequences) and a unique second targeting arm (e.g., they all have different sequences). In some embodiments, for at least 10% of the probes (e.g., at least 25%, 25%-50%, 50%-75%, 75%-90%, 90%-95% or over 95%, or all of the probes) the first targeting arm has a Tm for its complementary sequence that is higher (e.g., about 1 °C, about 2 °C, about 3 °C, about 4 °C, about 5 °C, or more than about 5 °C higher) than the Tm of the second targeting arm for its complementary sequence. In some embodiments, each of the first targeting arms have similar or identical Tms for their respective complementary sequences and each of the second targeting arms have similar or identical Tms for their respective complementary sequences (and the first targeting arms have higher Tms than the second targeting arms). For example, in some embodiments, the Tm of the first arm(s) may be about 58 °C and the Tm of the second arm(s) may be about 56 °C. In some embodiments, the Tm of the first arm(s) may be about 68 °C, and the Tm of the second arm(s) may be about 65 °C. It should be appreciated that in some embodiments the similarity (e.g., within a range of 1 °C, 2 °C, 3 °C, 4 °C, 5 °C) or identity of the Tms for the different targeting arms should be based either on empirical data for each arm or based on the same predictive algorithm for each arm (e.g., Wallace,R.B., Shaffer,J., Murphy,R.F., Bonner,J., Hirose,T., and Itakura,K. (1979) Nucleic Acids Res 6:3543-3557, SantaLucia J (1998), Proc Natl Acad Sci USA, 95:1460-5, or other algorithm).

In some embodiments, the Tm of the first targeting arm of a molecular inversion probe (at the 5' end of the molecular inversion probe) is selected to be sufficiently stable to prevent displacement of the first targeting arm from its complementary sequence on a target nucleic acid. In some embodiments, the Tm of the first targeting arm is 50-55 °C, at least 55 °C, 55-60 °C, at least 60 °C, 60-65 °C, at least 65 °C, at least 70 °C, at least 75 °C, or at least 80 °C. As discussed above, it should be appreciated that the for a particular targeting arm may be determined empirically or theoretically. Different theoretical models may be used to determine a Tm and it should be appreciated that the predicted Tm for a particular sequence may be different depending on the algorithm used for the prediction. In some embodiments, each probe in a plurality of probes (e.g., each probe in a set of 5-10, each probe in a set of at least 10, each probe in a set of 10-50, each

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probe in a set of 50-100, each probe in a set of 100-500, or each probe in a set of at least 500 different probes) has a different first targeting arm (e.g., different sequences) but each different first targeting arm has a similar or identical Tm for its complementary sequence on a target nucleic acid. It should be appreciated that in some embodiments the similarity (e.g., within a range of 1 C, 2 C, 3 C, 4 C, 5 C) or identity of the Tms for the different targeting arms should be based either on empirical data for each arm or based on the same predictive algorithm for each arm (e.g., Wallace,R.B., Shaffer,J., Murphy,R.F., Bonner,J., Hirose,T., and Itakura,K. (1979) Nucleic Acids Res 6:3543-3557, SantaLucia J (1998), Proc Natl Acad Sci USA, 95:1460-5, or other algorithm).

In some embodiments, the sub-target nucleic acid contains a nucleic acid repeat. In some embodiments, the nucleic acid repeat is a dinucleotide or trinucleotide repeat. In some embodiments, the sub-target nucleic acid contains 10-100 copies of the nucleic acid repeat in the absence of an abnormal increase or decrease in nucleic acid repeats. In some embodiments, the sub-target nucleic acid is a region of the Fragile-X locus that contains a nucleic acid repeat. In some embodiments, one or both targeting arms hybridize to a region on the target nucleic acid that is immediately adjacent to a region of nucleic acid repeats. In some embodiments, one or both targeting arms hybridize to a region on the target nucleic acid that is separated from a region of nucleic acid repeats by a region that does not contain any nucleic acid repeats. In some embodiments, the molecular inversion probe further comprises a primer-binding region that can be used to sequence the captured sub-target nucleic acid and optionally the first and/or second targeting arm.

In some embodiments, aspects of the invention relate to evaluating the length of a plurality of different target nucleic acids in a biological sample. In some embodiments, the plurality of target nucleic acids are analyzed using a plurality of different molecular inversion probes. In some embodiments, each different molecular inversion probe comprises a different pair of first and second targeting arms at each of the 3' and 5' ends. In some embodiments, each different molecular inversion probe comprises the same primer-binding sequence.

In some embodiments, aspects of the invention relate to analyzing nucleic acid from a biological sample obtained from a subject. In some embodiments, the biological sample is a blood sample. In some embodiments, the biological sample is a tissue sample, specific cell population, tumor sample, circulating tumor cells, or environmental

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sample. In some embodiments, the biological sample is a single cell. In some embodiments, nucleic acids are analyzed in biological samples obtained from a plurality of different subjects. In some embodiments, nucleic acids from a biological sample are analyzed in multiplex reactions. It should be appreciated that a biological sample contains a plurality of copies of a genome derived from a plurality of cells in the sample. Accordingly, a sample may contain a plurality of independent copies of a target nucleic acid region of interest, the capture efficiency of which can be used to evaluate its size as described herein.

In some embodiments, aspects of the invention relate to evaluating a nucleic acid capture efficiency by determining an amount of target nucleic acid that is captured (e.g., an amount of sub-target nucleic acid sequences that are captured). In some embodiments, the amount of target nucleic acid that is captured is determined by determining a number of independently captured target nucleic acid molecules (e.g., the amount of independently captured molecules that have the sequence of the sub-target region). In some embodiments, the amount of target nucleic acid that is captured is compared to a reference amount of captured nucleic acid. In some embodiments, the reference amount is determined by determining a number of independently captured molecules of a reference nucleic acid. In some embodiments, the reference nucleic acid is a nucleic acid of a different locus in the biological sample that is not suspected of containing a deletion or insertion. In some embodiments, the reference nucleic acid is a nucleic acid of known size and amount that is added to the capture reaction. As described herein, a number of independently captured nucleic acid sequences can be determined by contacting a nucleic acid sample with a preparation of a probe (e.g., a MIP probe as described herein). It should be appreciated that the preparation may comprise a plurality of copies of the same probe and accordingly a plurality of independent copies of the target region may be captured by different probe molecules. The number of probe molecules that actually capture a sequence can be evaluated by determining an amount or number of captured molecules using any suitable technique. This number is a reflection of both the number of target molecules in the sample and the efficiency of capture of those target molecules, which in turn is related to the size of the target molecules as described herein. Accordingly, the capture efficiency can be evaluated by controlling for the abundance of the target nucleic acid, for example by comparing the number or amount of captured target molecules to an appropriate control (e.g., a known size and

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amount of control nucleic acid, or a different locus that should be present in the same amount in the biological sample and is not expected to contain any insertions or deletions). It should be appreciated that other factors may affect the capture efficiency of a particular target nucleic acid region (e.g., the sequence of the region, the GC content, the presence of secondary structures, etc.). However, these factors also can be accounted for by using appropriate controls (e.g., known sequences having similar properties, the same sequences, other genomic sequences expected to be present in the biological sample at the same frequency, etc., or any combination thereof).

In some embodiments, aspects of the invention relate to identifying a subject as having an insertion or deletion in one or more alleles of a genetic locus if the capture efficiency for that genetic locus is statistically significantly different than a reference capture efficiency.

It should be appreciated that hybridization conditions used for any of the capture techniques described herein (e.g., MIP capture techniques) can be based on known hybridization buffers and conditions.

In some embodiments, the methods disclosed herein are useful for any application where the detection of deletions or insertions is important.

In some embodiments, aspects of the invention relate to basing a nucleic acid sequence analysis on results from two or more different nucleic acid preparatory techniques that have different systematic biases in the types of nucleic acids that they sample. According to the invention, different techniques have different sequence biases that are systematic and not simply due to stochastic effects during nucleic acid capture or amplification. Accordingly, the degree of oversampling required to overcome variations in nucleic acid preparation needs to be sufficient to overcome the biases (e.g., an oversampling of 2-5 fold, 5-10 fold, 5-15 fold, 15-20 fold, 20-30 fold, 30-50 fold, or intermediate to higher fold).

According to some embodiments, different techniques have different characteristic or systematic biases. For example, one technique may bias a sample analysis towards one particular allele at a genetic locus of interest, whereas a different technique would bias the sample analysis towards a different allele at the same locus. Accordingly, the same sample may be identified as being different depending on the type of technique that is used to prepare nucleic acid for sequence analysis. This effectively

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represents a sensitivity limitation, because each technique has different relative sensitivities for polymorphic sequences of interest.

According to aspects of the invention, the sensitivity of a nucleic acid analysis can be increased by combining the sequences from different nucleic acid preparative steps and using the combined sequence information for a diagnostic assay (e.g., for a making a call as to whether a subject is homozygous or heterozygous at a genetic locus of interest).

In some embodiments, the invention provides a method of increasing the sensitivity of a nucleic acid detection assay by obtaining a first preparation of a target nucleic acid using a first preparative method on a biological sample, obtaining a second preparation of a target nucleic acid using a second preparative method on the biological sample, assaying the sequences obtained in both first and second nucleic acid preparations, and using the sequence information from both first and second nucleic acid preparations to determine the genotype of the target nucleic acid in the biological sample, wherein the first and second preparative methods have different systematic sequence biases. In some embodiments, the first and second nucleic acid preparations are combined prior to performing a sequence assay. In some embodiments, separate sequence assays are performed on the first and second nucleic acid preparations and the sequence information from both assays are combined to determine the genotype of the target nucleic acid in the biological sample. In some embodiments, the first preparative method is an amplification-based, a hybridization-based, or a circular probe-based preparative method. In some embodiments, the second method is an amplification-based, a hybridization-based, or a circular probe-based preparative method. In some embodiments, the first and second methods are of different types (e.g., only one of them is an amplification-based, a hybridization-based, or a circular probe-based preparative method, and the other one is one or the other two types of method). Accordingly, in some embodiments the second preparative method is an amplification-based, a hybridization-based, or a circular probe-based preparative method, provided that the second method is different from the first method. However, in some embodiments, both methods may be of the same type, provided they are different methods (e.g., both are amplification based or hybridization-based, but are different types of amplification or hybridization methods, e.g., with different relative biases).

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In amplification-based (e.g., PCR-based or LCR-based, etc.) preparative methods, genomic loci (target nucleic acids) are isolated directly by means of a polymerase chain reaction or ligase chain reaction (or other amplification method) that selectively amplifies each locus using a pair of oligonucleotide primers. It is to be understood that primers will be sufficiently complementary to the target sequence to hybridize with and prime amplification of the target nucleic acid. Any one of a variety of art known methods may be utilized for primer design and synthesis. One or both of the primers may be perfectly complementary to the target sequence. Degenerate primers may also be used. Primers may also include additional nucleic acids that are not complementary to target sequences but that facilitate downstream applications, including for example restriction sites and identifier sequences (e.g., source sequences). PCR based methods may include amplification of a single target nucleic acid and multiplex amplification (amplification of multiple target nucleic acids in parallel).

Hybridization-based preparative may methods involve selectively immobilizing target nucleic acids for further manipulation. It is to be understood that one or more oligonucleotides (immobilization oligonucleotides), which in some embodiments may be from 10 to 200 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it. In some embodiments, immobilization oligonucleotides are either immobilized before hybridization is performed (e.g., Roche/Nimblegen 'sequence capture'), or are prepared such that they include a moiety (e.g., biotin) which can be used to selectively immobilize the target nucleic acid after hybridization by binding to e.g., streptavidin-coated microbeads (e.g., Agilent 'SureSelect').

Circularization selection-based preparative methods selectively convert each region of interest into a covalently-closed circular molecule which is then isolated by removal (usually enzymatic, e.g., with exonuclease) of any non-circularized linear nucleic acid. Oligonucleotide probes are designed which have ends that flank the region of interest. The probes are allowed to hybridize to the genomic target, and enzymes are used to first (optionally) fill in any gap between probe ends and second ligate the probe closed. In some embodiments, following circularization, any remaining (non-target) linear nucleic acid can be removed, resulting in isolation (capture) of target nucleic acid. Circularization selection-based preparative methods include molecular inversion probe capture reactions and 'selector' capture reactions. However, other techniques may be

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used as aspects of the invention are not limited in this respect. In some embodiments, molecular inversion probe capture of a target nucleic acid is indicative of the presence of a polymorphism in the target nucleic acid.

A variety of methods may be used to evaluate and compare bias profiles of each preparative technique. Next-generation sequencing may be used to quantitatively measure the abundance of each isolated target nucleic acid obtained from a certain preparative method. This abundance may be compared to a control abundance value (e.g., a known starting abundance of the target nucleic acid) and/or with an abundance determined through the use of an alternative preparative method. For example, a set of target nucleic acids may be isolated by one or more of the three preparative methods; the target nucleic acid may be observed x times using the amplification technique, y times using the hybridization enrichment technique, and z times using the circularization selection technique. A pairwise correlation coefficient may be computed between each abundance value (e.g., x and y, x and z, and y and z) to assess bias in nucleic acid isolation between pairs of preparative methods. Since the mechanisms of isolation are different in each approach, the abundances will usually be different and largely uncorrelated with each other.

In some embodiments, the invention provides a method of obtaining a nucleic acid preparation that is representative of a target nucleic acid in a biological sample by obtaining a first preparation of a target nucleic acid using a first preparative method on a biological sample, obtaining a second preparation of a target nucleic acid using a second preparative method on the biological sample, and combining the first and second nucleic acid preparations to obtain a combined preparation that is representative of the target nucleic acid in the biological sample.

In some embodiments of any of the methods described herein, a third preparation of the target nucleic acid is obtained using a third preparative method that is different from the first and second preparative methods, wherein the first, second, and third preparative methods all have different systematic sequence biases. In some embodiments of any of the methods described herein, the different preparative methods are used for a plurality of different loci in the biological sample to increase the sensitivity of a multiplex nucleic acid analysis. In some embodiments, the target nucleic acid has a sequence of a gene selected from Table 1.

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However, it should be appreciated that a genotyping method of the invention may include several steps, each of which independently may involve one or more different preparative techniques described herein. In some embodiments, a nucleic acid preparation may be obtained using one or more (e.g., 2, 3, 4, 5, or more) different techniques described herein (e.g., amplification, hybridization capture, circular probe capture, etc., or any combination thereof) and the nucleic acid preparation may be analyzed using one or more different techniques (e.g., amplification, hybridization capture, circular probe capture, etc., or any combination thereof) that are selected independently of the techniques used for the initial preparation.

In some embodiments, aspects of the invention also provide compositions, kits, devices, and analytical methods for increasing the sensitivity of nucleic acid assays. Aspects of the invention are particularly useful for increasing the confidence level of genotyping analyses. However, aspects of the invention may be used in the context of any suitable nucleic acid analysis, for example, but not limited to, a nucleic acid analysis that is designed to determine whether more than one sequence variant is present in a sample.

In some embodiments, aspects of the invention relate to a plurality of nucleic acid probes (e.g., 10-50, 50-100, 100-250, 250-500, 500-1,000, 1,000-2,000, 2,000-5,000, 5,000-7,500, 7,500-10,000, or lower, higher, or intermediate number of different probes). In some embodiments, each probe or each of a subset of probes (e.g., 10-25%, 25-50%, 50-75%, 75-90%, or 90-99%) has a different first targeting arm. In some embodiments, each probe or each probe of a subset of probes (e.g., 10-25%, 25-50%, 50-75%, 75-90%, or 90-99%) has a different second targeting arm. In some embodiments, the first and second targeting arms are separated by the same intervening sequence. In some embodiments, the first and second targeting arms are complementary to target nucleic acid sequences that are separated by the same or a similar length (e.g., number of nucleic acids, for example, 0-25, 25-50, 50-100, 100-250, 250-500, 500-1,000, 1,000-2,500 or longer or intermediate number of nucleotides) on their respective target nucleic acids (e.g., genomic loci). In some embodiments, each probe or a subset of probes (e.g., 10-25%, 25-50%, 50-75%, 75-90%, or 90-99%) includes a first primer binding sequence. In some embodiments, the primer binding sequence is the same (e.g., it can be used to prime sequencing or other extension reaction). In some embodiments, each probe or a subset of probes (e.g., 10-25%, 25-50%, 50-75%, 75-90%, or 90-99%) includes a unique

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identifier sequence tag (e.g., that is predetermined and can be used to distinguish each probe).

In some embodiments, the methods disclosed herein are useful for any application where sensitivity is important. For example, detection of cancer mutations in a heterogenous tissue sample, detection of mutations in maternally-circulating fetal DNA, and detection of mutations in cells isolated during a preimplantation genetic diagnostic procedure.

According to some aspects of the invention, methods of detecting a polymorphism in a nucleic acid in a biological sample are provided. In some embodiments, the methods comprise obtaining a nucleic acid preparation using a preparative method (e.g., any of the preparative methods disclosed herein) on a biological sample, and performing a molecular inversion probe capture reaction on the nucleic acid preparation, wherein a molecular inversion probe capture (e.g., using a mutation-detection MIP) of a target nucleic acid of the nucleic acid preparation is indicative of the presence of a mutation (polymorphism) in the target nucleic acid, optionally wherein the polymorphism is selected from Table 2.

According to some aspects of the invention, methods of genotyping a nucleic acid in a biological sample are provided. In some embodiments, the methods comprise obtaining a nucleic acid preparation using a preparative method on a biological sample, sequencing a target nucleic acid of the nucleic acid preparation, and performing a molecular inversion probe capture reaction on the biological sample, wherein a molecular inversion probe capture of the target nucleic acid in the biological sample is indicative of the presence of a polymorphism in the target nucleic acid, genotyping the target nucleic acid based on the results of the sequencing and the capture reaction.

In some embodiments of the methods disclosed herein, the target nucleic acid has a sequence of a gene selected from Table 1.

It should be appreciated that any one or more embodiments described herein may be used for evaluating multiple genetic markers in parallel. Accordingly, in some embodiments, aspects of the invention relate to determining the presence of one or more markers (e.g., one or more alleles) at multiple different genetic loci in parallel. Accordingly, the risk or presence of multiple heritable disorders may be evaluated in parallel. In some embodiments, the risk of having offspring with one or more heritable

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disorders may be evaluated. In some embodiments, an evaluation may be performed on a biological sample of a parent or a child (e.g., at a pre-implantation, prenatal, perinatal, or postnatal stage). In some embodiments, the disclosure provides methods for analyzing multiple genetic loci (e.g., a plurality of target nucleic acids selected from Table 1 or 2) from a patient sample, such as a blood, pre-implantation embryo, chorionic villus or amniotic fluid sample. A patient or subject may be a human. However, aspects of the invention are not limited to humans and may be applied to other species (e.g., mammals, birds, reptiles, other vertebrates or invertebrates) as aspects of the invention are not limited in this respect. A subject or patient may be male or female. In some embodiments, in connection with reproductive genetic counseling, samples from a male and female member of a couple may be analyzed. In some embodiments, for example, in connection with an animal breeding program, samples from a plurality of male and female subjects may be analyzed to determine compatible or optimal breeding partners or strategies for particular traits or to avoid one or more diseases or conditions. Accordingly, reproductive risks may be determined and/or reproductive recommendations may be provided based on information derived from one or more embodiments of the invention.

However, it should be appreciated that aspects of the invention may be used in connection with any medical evaluation where the presence of one or more alleles at a genetic locus of interest is relevant to a medical determination (e.g., risk or detection of disease, disease prognosis, therapy selection, therapy monitoring, etc.). Further aspects of the invention may be used in connection with detection, in tumor tissue or circulating tumor cells, of mutations in cellular pathways that cause cancer or predict efficacy of treatment regimens, or with detection and identification of pathogenic organisms in the environment or a sample obtained from a subject, *e.g.*, a human subject.

These and other aspects of the invention are described in more detail in the following description and non-limiting examples and drawings.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 illustrates a non-limiting embodiment of a tiled probe layout;

FIG. 2 illustrates a non-limiting embodiment of a staggered probe layout;

FIG. 3 illustrates a non-limiting embodiment of an alternating staggered probe layout;

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FIGs. 4A, B, and C depict various non-limiting methods for combining differentiator tag sequence and target sequences (NNNN depicts a differentiator tag sequence);

FIG. 5 depicts a non-limiting method for genotyping based on target and differentiator tag sequences;

FIG. 6 depicts non-limiting results of a simulation of a MIP capture reaction;

FIG. 7 depicts a non-limiting graph of sequencing coverage;

FIG. 8 illustrates that shorter sequences are captured with higher efficiency that longer sequences using MIPs;

FIG. 9 illustrates a non-limiting scheme of padlock (MIP) capture of a region that includes both repetitive regions (thick wavy line) and the adjacent unique sequence (thick strait line);

FIG. 10 illustrates a non-limiting hypothetical relationship between target gap size and the relative number of reads of the repetitive region;

FIG. 11A depicts MIP capture of FMR1 repeat regions from a diploid genome;

FIG. 11B depicts preparative methods for biallelic resolution of FMR1 repeat region lengths in a diploid genome using MIP capture probes and unique differentiator tags;

FIG. 11C depicts an analysis of FMR1 repeat region lengths in a diploid genome;

FIG. 12 is a schematic of an embodiment of an algorithm of the invention;

FIG. 13 illustrates a non-limiting example of a graph of per-target abundance with MIP capture; and,

FIG. 14 shows a non-limiting a graph of correlation between two MIP capture reactions.

DETAILED DESCRIPTION

Aspects of the invention relate to preparative and analytical methods and compositions for evaluating genotypes, and in particular, for determining the allelic identity (or identities in a diploid organism) of one or more genetic loci in a subject. Aspects of the invention are based, in part, on the identification of different sources of ambiguity and error in genetic analyses, and, in part, on the identification of one or more approaches to avoid, reduce, recognize, and/or resolve these errors and ambiguities at different stages in a genetic analysis. Aspects of the invention relate to methods and

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compositions for addressing bias and/or stochastic variation associated with one or more preparative and/or analytical steps of a nucleic acid evaluation technology. In some embodiments, preparative methods can be adapted to avoid or reduce the risk of bias skewing the results of a genetic analysis. In some embodiments, analytical methods can be adapted to recognize and correct for data variations that may give rise to misinterpretation (e.g., incorrect calls such as homozygous when the subject is actually heterozygous or heterozygous when the subject is actually homozygous). Methods of the invention may be used for any type of mutation, for example a single base change (e.g., insertion, deletion, transversion or transition, etc.), a multiple base insertion, deletion, duplication, inversion, and/or any other change or combination thereof.

In some embodiments, additional or alternative techniques may be used to address loci characterized by multiple repeats of a core sequence where the length of the repeat is longer than a typical sequencing read thereby making it difficult to determine whether a deletion or duplication of one or more core sequence units has occurred based solely on a sequence read.

In some embodiments, increased confidence in an assay result may be obtained by i) selecting two or more different preparative and/or analytical techniques that have different biases (e.g., known to have different biases), ii) evaluating a patient sample using the two or more different techniques, iii) comparing the results from the two or more different techniques, and/or iv) determining whether the results are consistent for the two or more different techniques. In some embodiments, if determining in step (iv) indicates that the results are consistent (e.g., the same) then increased confidence in the assay result is obtained. In other embodiments, if determining in step (iv) indicates that the results are inconsistent (e.g., that the results are ambiguous) then one or more additional preparative and/or analytical techniques, which have a different bias (e.g., known to have a different bias) compared with the two or more different preparative and/or analytical techniques selected in step (i), are used to evaluate the patient sample, and the results of the one or more additional preparative and/or analytical techniques are compared with the results from step (ii) to resolve the inconsistency.

In some embodiments, two or more independent samples may be obtained from a subject and independently analyzed. In some embodiments, two or more independent samples are obtained at approximately the same time point. In some embodiments, two or more independent samples are obtained at multiple different time points. In some

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embodiments, the use of two or more independent sample facilitates the elimination, normalization, and/or quantification of stochastic measurement noise. It is to be appreciated that two or more independent samples may be obtained in connection with any of the methods disclosed herein, including, for example, methods for pathogen profiling in a human or other animal subjects, monitoring tumor progression/regression, analyzing circulating tumor cells, analyzing fetal cells in maternal circulation, and analyzing/monitoring/profiling of environmental pathogens.

In some embodiments, one or more of the techniques described herein may be combined in a single assay protocol for evaluating multiple patient samples in parallel.

It should be appreciated that aspects of the invention may be useful for high throughput, cost-effective, yet reliable, genotyping of multiple patient samples (e.g., in parallel, for example in multiplex reactions). In some embodiments, aspects of the invention are useful to reduce the error frequency in a multiplex analysis. Certain embodiments may be particularly useful where multiple reactions (e.g., multiple loci and/or multiple patient samples) are being processed. For example, 10-25, 25-50, 50-75, 75-100 or more loci may be evaluated for each subject out of any number of subject samples that may be processed in parallel (e.g., 1-25, 25-50, 50-100, 100-500, 500-1,000, 1,000-2,500, 2,500-5,000 or more or intermediate numbers of patient samples). It should be appreciated that different embodiments of the invention may involve conducting two or more target capture reactions and/or two or more patient sample analyses in parallel in a single multiplex reaction. For example, in some embodiments a plurality of capture reactions (e.g., using different capture probes for different target loci) may be performed in a single multiplex reaction on a single patient sample. In some embodiments, a plurality of captured nucleic acids from each one of a plurality of patient samples may be combined in a single multiplex analysis reaction. In some embodiments, samples from different subjects are tagged with subject-specific (e.g., patient-specific) tags (e.g., unique sequence tags) so that the information from each product can be assigned to an identified subject. In some embodiments, each of the different capture probes used for each patient sample have a common patient-specific tag. In some embodiments, the capture probes do not have patient-specific tags, but the captured products from each subject may be amplified using one or a pair of amplification primers that are labeled with a patient-specific tag. Other techniques for associating a patient-specific tag with the captured product from a single patient sample may be used as aspects of the

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invention are not limited in this respect. It should be appreciated that patient-specific tags as used herein may refer to unique tags that are assigned to identified patients in a particular assay. The same tags may be used in a separate multiplex analysis with a different set of patient samples (e.g., from different patients) each of which is assigned one of the tags. In some embodiments, different sets of unique tags may be used in sequential (e.g., alternating) multiplex reactions in order to reduce the risk of contamination from one assay to the next and allow contamination to be detected on the basis of the presence of tags that are not expected to be present in a particular assay.

Embodiments of the invention may be used for any of a number of different settings: reproductive settings, disease screening, identifying subjects having cancer, identifying subjects having increased risk for a disease, stratifying a population of subjects according to one or more of a number of factors, for example responsiveness to a particular drug, lack or not of an adverse reaction (or risk therefore) to a particular drug, and/or providing information for medical records (e.g., homozygosity, heterozygosity at one or more loci). It should be appreciated that the invention is not limited to genomic analysis of patient samples. For example, aspects of the invention may be useful for high throughput genetic analysis of environment samples to detect pathogens.

In some embodiments, the methods disclosed herein are useful for diagnosis of one or more heritable disorders. In some embodiments, a heritable disorder that may be diagnosed with the methods disclosed herein is a genetic disorder that is prevalent in the Ashkenazi Jewish population. In some embodiments, the heritable disorders are selected from: 21-Hydroxylase-Defiocient Congenital Adrenal Hyperplasia; ABCC8-Related Hyperinsulinism; Alpha-Thalassemia, includes Constant Spring, & MR associated; Arylsulfatase A Deficiency-Metyachromatic Leukodystrophy; Biotinidase Deficiency-Holocarboxylase Synthetase Deficiency; Bloom's Syndrome; Canavan Disease; CFTR-Related Disorders-cystic fibrosis; Citrullinemia Type I; Combined MMA & Homocystinuria-dblC; Dystrophinopathies (DMD & BMD); Familial Dysautonomia; Fanconi Anemia-FANCC; Galactosemia-Classical: Galactokinase Defiency & Galactose Epimerase Deficiency; Gaucher Disease; GJB2-Related DFNB 1 Nonsyndromic Hearing Loss and Deafness; Glutaric acidemia Type 1; Hemoglobinopathies beta-chain disorders; Glycogen Storage Disease Type 1A; Maple Syrup Urine Disease; Types 1A, 1B, 2, 3; Medium Chain Acyl-Coenzyme A; Dehydrogenase Deficiency-MCADD;

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Methylmalonic Acidemia; Mucolipidosis IV; Nemaline Myopathy; Nieman-Pick Type A-Acid Sphingomyelinase Deficiency; Non-Ketotic Hyperglycinemia-Glycine Encephalopathy; Ornithine Transcarbamylase Deficiency; PKU Phenylalanine Hydroxylase Deficiency; Propionic Acidemia; Short Chain Acyl-CoA Dehydrogenase Deficiency-SCADD; Smith-Lemli-Opitz Syndrome; Spinal Muscular Atrophy (SMN1)-SMA; Tay Sachs-HexA Deficiency; Usher Synbdrome-Type I (Type IB, Type IC, Type ID, Type IF, Type IG) ; X-Linked Mental Retardation ARX-Related Disorders; X-Linked Mental Retardation with Cerebellar Cypoplasia and sistinctive Facial Appearance; X-Linked Mental Retardation; includes 9, 21, 30, 46, 58, 63, 88, 89; X-linked mental retardation: FM1-Related Disorders-FRXA, Fragile X MR; X-linked SMR: Renpenning Syndrome 1; Zellweger Spectrum disorders - Peroxisomal Bifunctional Enzyme Deficiencies including Zellweger, NALD, and/or infantile Refsums. However, all of these, subsets of these, other genes, or combinations thereof may be used.

According to some aspects, the disclosure relates to multiplex diagnostic methods. In some embodiments, multiplex diagnostic methods comprise capturing a plurality of genetic loci in parallel (e.g., a genetic locus of Table 1). In some embodiments, genetic loci possess one or more polymorphisms (e.g., a polymorphism of Table 2) the genotypes of which correspond to disease causing alleles. Accordingly, in some embodiments, the disclosure provides methods for assessing multiple heritable disorders in parallel.

In some embodiments, methods are provided for diagnosing multiple heritable disorders in parallel at a pre-implantation, prenatal, perinatal, or postnatal stage. In some embodiments, the disclosure provides methods for analyzing multiple genetic loci (e.g., a plurality of target nucleic acids selected from Table 1) from a patient sample, such as a blood, pre-implantation embryo, chorionic villus or amniotic fluid sample. A patient or subject may be a human. However, aspects of the invention are not limited to humans and may be applied to other species (e.g., mammals, birds, reptiles, other vertebrates or invertebrates) as aspects of the invention are not limited in this respect. A subject or patient may be male or female. In some embodiments, in connection with reproductive genetic counseling, samples from a male and female member of a couple may be analyzed. In some embodiments, for example, in connection with an animal breeding program, samples from a plurality of male and female subjects may be analyzed to

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determine compatible or optimal breeding partners or strategies for particular traits or to avoid one or more diseases or conditions.

However, it should be appreciated that any other diseases may be studied and/or risk factors for diseases or disorders including, but not limited to allergies, responsiveness to treatment, cancer tumor profiling for treatment and prognosis, monitoring and identification of patient infections, and monitoring of environmental pathogens.

1. Reducing representational bias in multiplex amplification reactions:

In some embodiments, aspects of the invention relate to methods that reduce bias and increase reproducibility in multiplex detection of genetic loci, e.g., for diagnostic purposes.

Molecular inversion probe technology is used to detect or amplify particular nucleic acid sequences in potentially complex mixtures. Use of molecular inversion probes has been demonstrated for detection of single nucleotide polymorphisms (Hardenbol et al. 2005 Genome Res 15:269-75) and for preparative amplification of large sets of exons (Porreca et al. 2007 Nat Methods 4:931-6, Krishnakumar et al. 2008 Proc Natl Acad Sci USA 105:9296-301). One of the main benefits of the method is in its capacity for a high degree of multiplexing, because generally thousands of targets may be captured in a single reaction containing thousands of probes. However, challenges associated with, for example, amplification efficiency (See, e.g., Turner EH, et al., Nat Methods. 2009 Apr 6:1-2.) have limited the practical utility of the method in research and diagnostic settings.

Aspects of the disclosure are based, in part, on the discovery of effective methods for overcoming challenges associated with systematic errors (bias) in multiplex genomic capture and sequencing methods, namely high variability in target nucleic acid representation and unequal sampling of heterozygous alleles in pools of captured target nucleic acids (e.g., isolated from a biological sample). Accordingly, in some embodiments, the disclosure provides methods that reduce variability in the detection of target nucleic acids in multiplex capture methods. In other embodiments, methods improve allelic representation in a capture pool and, thus, improve variant detection outcomes. In certain embodiments, the disclosure provides preparative methods for capturing target nucleic acids (e.g., genetic loci) that involve the use of different sets of

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multiple probes (e.g., molecular inversion probes MIPs) that capture overlapping regions of a target nucleic acid to achieve a more uniform representation of the target nucleic acids in a capture pool compared with methods of the prior art. In other embodiments, methods reduce bias, or the risk of bias, associated with large scale parallel capture of genetic loci, e.g., for diagnostic purposes. In other embodiments, methods are provided for increasing reproducibility (e.g., by reducing the effect of polymorphisms on target nucleic acid capture) in the detection of a plurality of genetic loci in parallel. In further embodiments, methods are provided for reducing the effect of probe synthesis and/or probe amplification variability on the analysis of a plurality of genetic loci in parallel.

In some aspects, the disclosure provides probe sets that comprise a plurality of different probes. As used herein, a 'probe' is a nucleic acid having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids flanking the same strand of a target nucleic acid or subregion thereof. An exemplary probe is a molecular inversion probe (MIP). A 'target nucleic acid' may be a genetic locus. Exemplary genetic loci are disclosed herein in Table 1 (RefSeqGene Column).

While probes have been typically designed to meet certain constraints (e.g. melting temperature, G/C content, etc.) known to partially affect capture/amplification efficiency (Ball et al (2009) Nat Biotech 27:361-8 AND Deng et al (2009) Nat Biotech 27:353-60), a set of constraints which is sufficient to ensure either largely uniform or highly reproducible capture/amplification efficiency has not previously been achieved. As disclosed herein, uniformity and reproducibility can be increased by designing multiple probes per target, such that each base in the target is captured by more than one probe. In some embodiments, the disclosure provides multiple MIPs per target to be captured, where each MIP in a set designed for a given target nucleic acid has a central region and a 5' region and 3' region ('targeting arms') which hybridize to (at least partially) different nucleic acids in the target nucleic acid (immediately flanking a subregion of the target nucleic acid). Thus, differences in efficiency between different targeting arms and fill-in sequences may be averaged across multiple MIPs for a single target, which results in more uniform and reproducible capture efficiency.

In some embodiments, the methods involve designing a single probe for each target (a target can be as small as a single base or as large as a kilobase or more of contiguous sequence).

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It may be preferable, in some cases, to design probes to capture molecules (e.g., target nucleic acids or subregions thereof) having lengths in the range of 1 - 200 bp (as used herein, a bp refers to a base pair on a double-stranded nucleic acid – however, where lengths are indicated in bps, it should be appreciated that single-stranded nucleic acids having the same number of bases, as opposed to base pairs, in length also are contemplated by the invention). However, probe design is not so limited. For example, probes can be designed to capture targets having lengths in the range of up to 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 1000, or more bps, in some cases.

It is to be appreciated that the length of a capture molecule (e.g., a target nucleic acid or subregion thereof) is selected based upon multiple considerations. For example, where analysis of a target involves sequencing, e.g., with a next-generation sequencer, the target length should typically match the sequencing read-length so that shotgun library construction is not necessary. However, it should be appreciated that captured nucleic acids may be sequenced using any suitable sequencing technique as aspects of the invention are not limited in this respect.

It is also to be appreciated that some target nucleic acids are too large to be captured with one probe. Consequently, it may be necessary to capture multiple subregions of a target nucleic acid in order to analyze the full target.

In some embodiments, a subregion of a target nucleic acid is at least 1 bp. In other embodiments, a subregion of a target nucleic acid is at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 bp or more. In other embodiments, a subregion of a target nucleic acid has a length that is up to 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or more percent of a target nucleic acid length.

The skilled artisan will also appreciate that consideration is made, in the design of MIPs, for the relationship between probe length and target length. In some embodiments, MIPs are designed such that they are several hundred basepairs (e.g., up to 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 bp or more) longer than corresponding target (e.g., subregion of a target nucleic acid, target nucleic acid).

In some embodiments, lengths of subregions of a target nucleic acid may differ. For example, if a target nucleic acid contains regions for which probe hybridization is not possible or inefficient, it may be necessary to use probes that capture subregions of

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one or more different lengths in order to avoid hybridization with problematic nucleic acids and capture nucleic acids that encompass a complete target nucleic acid.

Aspects of the invention involve using multiple probes, e.g., MIPs, to amplify each target nucleic acid. In some embodiments, the set of probes for a given target can be designed to 'tile' across the target, capturing the target as a series of shorter sub-targets. In some embodiments, where a set of probes for a given target is designed to 'tile' across the target, some probes in the set capture flanking non-target sequence). Alternately, the set can be designed to 'stagger' the exact positions of the hybridization regions flanking the target, capturing the full target (and in some cases capturing flanking non-target sequence) with multiple probes having different targeting arms, obviating the need for tiling. The particular approach chosen will depend on the nature of the target set. For example, if small regions are to be captured, a staggered-end approach might be appropriate, whereas if longer regions are desired, tiling might be chosen. In all cases, the amount of bias-tolerance for probes targeting pathological loci can be adjusted ('dialed in') by changing the number of different MIPs used to capture a given molecule.

In some embodiments, the 'coverage factor', or number of probes used to capture a basepair in a molecule, is an important parameter to specify. Different numbers of probes per target are indicated depending on whether one is using the tiling approach (see, e.g., FIG. 1) or one of the staggered approaches (see, e.g., FIGs. 2 or 3).

FIG. 1 illustrates a non-limiting embodiment of a tiled probe layout showing ten captured sub-targets tiled across a single target. Each position in the target is covered by three sub-targets such that MIP performance per base pair is averaged across three probes.

FIG. 2 illustrates a non-limiting embodiment of a staggered probe layout showing the targets captured by a set of three MIPs. Each MIP captures the full target, shown in black, plus (in some cases) additional extra-target sequence, shown in gray, such that the targeting arms of each MIP fall on different sequence. Each position in the target is covered by three sub-targets such that MIP performance per basepair is averaged across three probes. Targeting arms land immediately adjacent to the black or gray regions shown. It should be appreciated that in some embodiments, the targeting arms (not shown) can be designed so that they do not overlap with each other.

FIG. 3 illustrates a non-limiting embodiment of an alternating staggered probe layout showing the targets captured by a set of three MIPs. Each MIP captures the full

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target, shown in black, plus (in some cases) additional extra-target sequence, shown in gray, such that the targeting arms of each MIP fall on different sequence. Each position in the target is covered by three sub-targets such that MIP performance per basepair is averaged across three probes. Targeting arms land immediately adjacent to the black or gray regions shown.

It should be appreciated that for any of the layouts, the targeting arms on adjacent tiled or staggered probes may be designed to either overlap, not overlap, or overlap for only a subset of the probes.

In certain embodiments for any of the layouts, a coverage factor of about 3 to about 10 is used. However, the methods are not so limited and coverage factors of up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 20 or more may be used. It is to be appreciated that the coverage factor selected may depend the probe layout being employed. For example, in the tiling approach, for a desired coverage factor, the number of probes per target is typically a function of target length, sub-target length, and spacing between adjacent sub-target start locations (step size). For example, for a desired coverage factor of 3, a 200 bp target with a start-site separation of 20 bp and sub-target length of 60 bp may be encompassed with 12 MIPs (FIG. 1). Thus, a specific coverage factor may be achieved by varying the number of probes per target nucleic acid and the length of the molecules captured. In the staggered approach, a fixed-length target nucleic acid is captured as several subregions or as 'super-targets', which are molecules comprising the target nucleic acid and additional flanking nucleic acids, which may be of varying lengths. For example, a target of 50 bp can be captured at a coverage factor of 3 with 3 probes in either a 'staggered' (FIG. 2) or 'alternating staggered' configuration (FIG. 3).

The coverage factor will be driven by the extent to which detection bias is tolerable. In some cases, where the bias tolerance is small, it may be desirable to target more subregions of target nucleic acid with, perhaps, higher coverage factors. In some embodiments, the coverage factor is up to 2, 3, 4, 5, 6, 7, 8, 9, 10 or more.

In some embodiments, when a tiled probe layout is used, when the target length is greater than 1 bp and when a step size (distance between the 5'-end of a target and the 5' end of its adjacent target) is less than the length of a target or subregion thereof, it is possible to compute probe number for a particular target based on target length (T), sub-target length (S), and coverage factor (C), such that probe number = T/(S/C) + (C-1).

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In some aspects, the disclosure provides methods to increase the uniformity of amplification efficiency when multiple molecules are amplified in parallel; methods to increase the reproducibility of amplification efficiency; methods to reduce the contribution of targeting probe variability to amplification efficiency; methods to reduce the effect on a given target nucleic acid of polymorphisms in probe hybridization regions; and/or methods to simplify downstream workflows when multiplex amplification by MIPs is used as a preparative step for analysis by nucleic acid sequencing.

Polymorphisms in the target nucleic acid under the regions flanking a target can interfere with hybridization, polymerase fill-in, and/or ligation. Furthermore, this may occur for only one allele, resulting in allelic drop-out, which ultimately decreases downstream sequencing accuracy. In some embodiments, using a set of MIPs having multiple hybridization sites for the capture of any given target, the probability of loss from polymorphism is substantially decreased because not all targeting arms in the set of MIPs will cover the location of the mutation.

Probes for MIP capture reactions may be synthesized on programmable microarrays because of the large number of sequences required. Because of the low synthesis yields of these methods, a subsequent amplification step is required to produce sufficient probe for the MIP amplification reaction. The combination of multiplex oligonucleotide synthesis and pooled amplification results in uneven synthesis error rates and representational biases. By synthesizing multiple probes for each target, variation from these sources may be averaged out because not all probes for a given target will have the same error rates and biases.

Multiplex amplification strategies disclosed herein may be used analytically, as in detection of SNPs, or preparatively, often for next-generation sequencing or other sequencing techniques. In the preparative setting, the output of an amplification reaction is generally the input to a shotgun library protocol, which then becomes the input to the sequencing platform. The shotgun library is necessary in part because next-generation sequencing yields reads significantly shorter than amplicons such as exons. In addition to the bias-reduction afforded by the multi-tiled approach described here, tiling also obviates the need for shotgun library preparation. Since the length of the capture molecule can be specified when the probes, e.g., MIPs, are designed, it can be chosen to

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match the readlength of the sequencer. In this way, reads can 'walk' across an exon by virtue of the start position of each capture molecule in the probe set for that exon.

2. Reducing analytical errors associated with bias in nucleic acid preparations:

In some embodiments, aspects of the invention relate to preparative steps in DNA sequencing-related technologies that reduce bias and increase the reliability and accuracy of downstream quantitative applications.

There are currently many genomics assays that utilize next-generation (polony-based) sequencing to generate data, including genome resequencing, RNA-seq for gene expression, bisulphite sequencing for methylation, and Immune-seq, among others. In order to make quantitative measurements (including genotype calling), these methods utilize the counts of sequencing reads of a given genomic locus as a proxy for the representation of that sequence in the original sample of nucleic acids. The majority of these techniques require a preparative step to construct a high-complexity library of DNA molecules that is representative of a sample of interest. This may include chemical or biochemical treatment of the DNA (e.g., bisulphite treatment), capture of a specific subset of the genome (e.g., padlock probe capture, solution hybridization), and a variety of amplification techniques (e.g., polymerase chain reaction, whole genome amplification, rolling circle amplification).

Systematic and random errors are common problems associated with genome amplification and sequencing library construction techniques. For example, genomic sequencing library may contain an over- or under-representation of particular sequences from a source genome as a result of errors (bias) in the library construction process. Such bias can be particularly problematic when it results in target sequences from a genome being absent or undetectable in the sequencing libraries. For example, an under-representation of particular allelic sequences (e.g., heterozygotic alleles) from a genome in a sequencing library can result in an apparent homozygous representation in a sequencing library. As most downstream sequencing library quantification techniques depend on stochastic counting processes, these problems have typically been addressed by sampling enough (over-sampling) to obtain a minimum number of observations necessary to make statistically significant decisions. However, the strategy of oversampling is generally limited to elimination of low-count Poisson noise, and the

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approach wastes resources and increases the expense required to perform such experiments. Moreover, oversampling can result in a reduced statistical confidence in certain conclusions (e.g., diagnostic calls) based on the data. Accordingly, new approaches are needed for overcoming bias in sequencing library preparatory methods.

Aspects of the disclosure are based, in part, on the discovery of methods for overcoming problems associated with systematic and random errors (bias) in genome capture, amplification and sequencing methods, namely high variability in the capture and amplification of nucleic acids and disproportionate representation of heterozygous alleles in sequencing libraries. Accordingly, in some embodiments, the disclosure provides methods that reduce variability in the capture and amplification of nucleic acids. In other embodiments, the methods improve allelic representation in sequencing libraries and, thus, improve variant detection outcomes. In certain embodiments, the disclosure provides preparative methods for capturing target nucleic acids (e.g., genetic loci) that involve the use of differentiator tag sequences to uniquely tag individual nucleic acid molecules. In some embodiments, the differentiator tag sequence permits the detection of bias based on the frequency with which pairs of differentiator tag and target sequences are observed in a sequencing reaction. In other embodiments, the methods reduce errors caused by bias, or the risk of bias, associated with the capture, amplification and sequencing of genetic loci, e.g., for diagnostic purposes.

Aspects of the invention relate to associating unique sequence tags (referred to as differentiator tag sequences) with individual target molecules that are independently captured and/or analyzed (e.g., prior to amplification or other process that may introduce bias). These tags are useful to distinguish independent target molecules from each other thereby allowing an analysis to be based on a known number of individual target molecules. For example, if each of a plurality of target molecule sequences obtained in an assay is associated with a different differentiator tag, then the target sequences can be considered to be independent of each other and a genotype likelihood can be determined based on this information. In contrast, if each of the plurality of target molecule sequences obtained in the assay is associated with the same differentiator tag, then they probably all originated from the same target molecule due to over-representation (e.g., due to biased amplification) of this target molecule in the assay. This provides less information than the situation where each nucleic acid was associated with a different

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differentiator tag. In some embodiments, a threshold number of independently isolated molecules (e.g., unique combinations of differentiator tag and target sequences) is analyzed to determine the genotype of a subject.

In some embodiments, the invention relates to compositions comprising pools (libraries) of preparative nucleic acids that each comprise "differentiator tag sequences" for detecting and reducing the effects of bias, and for genotyping target nucleic acid sequences. As used herein, a "differentiator tag sequence" is a sequence of a nucleic acid (a preparative nucleic acid), which in the context of a plurality of different isolated nucleic acids, identifies a unique, independently isolated nucleic acid. Typically, differentiator tag sequences are used to identify the origin of a target nucleic acid at one or more stages of a nucleic acid preparative method. For example, in the context of a multiplex nucleic acid capture reaction, differentiator tag sequences provide a basis for differentiating between multiple independent, target nucleic acid capture events. Also, in the context of a multiplex nucleic acid amplification reaction, differentiator tag sequences provide a basis for differentiating between multiple independent, primary amplicons of a target nucleic acid, for example. Thus, combinations of target nucleic acid and differentiator tag sequence (target:differentiator tag sequences) of an isolated nucleic acid of a preparative method provide a basis for identifying unique, independently isolated target nucleic acids. FIG. 4A-C depict various non-limiting examples of methods for combining differentiator tag sequence and target sequences.

It will be apparent to the skilled artisan that differentiator tags may be synthesized using any one of a number of different methods known in the art. For example, differentiator tags may be synthesized by random nucleotide addition. Differentiator tag sequences are typically of a predefined length, which is selected to control the likelihood of producing unique target:differentiator tag sequences in a preparative reaction (e.g., amplification-based reaction, a circularization selection-based reaction, e.g., a MIP reaction). Differentiator tag sequences may be, up to 5, up to 6, up to 7 up to 8, up to 9, up to 10, up to 11, up to 12, up to 13, up to 14, up to 15, up to 16, up to 17, up to 18, up to 19, up to 20, up to 21, up to 22, up to 23, up to 24, up to 25, or more nucleotides in length. For purposes of genotyping, isolated nucleic acids are identified as independently isolated if they comprise unique combinations of target nucleic acid and differentiator tag sequences, and observance of threshold numbers of

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unique combinations of target nucleic acid and differentiator tag sequences provide a certain statistical confidence in the genotype.

During a library preparation process, each nucleic acid molecule may be tagged with a unique differentiator tag sequence in a configuration that permits the differentiator tag sequence to be sequenced along with the target nucleic acid sequence of interest (the nucleic acid sequence for which the library is being prepared, e.g., a polymorphic sequence). The incorporation of the nucleic acid comprising a differentiator tag sequence at a particular step allows the detection and correction of biases in subsequent steps of the protocol.

A large library of unique differentiator tag sequences may be created by using degenerate, random-sequence polynucleotides of defined length. The differentiator tag sequences of the polynucleotides may be read at the final stage of the sequencing. The observations of the differentiator tag sequences may be used to detect and correct biases in the final sequencing read-out of the library. For example, the total possible number of differentiator tag sequences, which may be produced, e.g., randomly, is 4^N, where N is the length of the differentiator tag sequence. Thus, it is to be understood that the length of the differentiator tag sequence may be adjusted such that the size of the population of MIPs having unique differentiator tag sequences is sufficient to produce a library of MIP capture products in which identical independent combinations of target nucleic acid and differentiator tag sequence are rare. As used herein combinations of target nucleic acid and differentiator tag sequences, may also be referred to as "target:differentiator tag sequences".

In the final readout of a sequencing process, each read may have an additional unique differentiator tag sequence. In some embodiments, when differentiator tag sequences are distributed randomly in a library, all the unique differentiator tag sequences will be observed about an equal number of times. Accordingly, the number of occurrences of a differentiator tag sequence may follow a Poisson distribution.

In some embodiments, overrepresentation of target:differentiator tag sequences in a pool of preparative nucleic acids (e.g., amplified MIP capture products) is indicative of bias in the preparative process (e.g., bias in the amplification process). For example, target:differentiator tag sequence combinations that are statistically overrepresented are indicative of bias in the protocol at one or more steps between the incorporation of the

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differentiator tag sequences into MIPs and the actual sequencing of the MIP capture products.

The number of reads of a given target:differentiator tag sequence may be indicative (may serve as a proxy) of the amount of that target sequence present in the originating sample. In some embodiments, the numbers of occurrence of sequences in the originating sample is the quantity of interest. For example, using the methods disclosed herein, the occurrence of differentiator tag sequences in a pool of MIPs may be predetermined (e.g., may be the same for all differentiator tag sequences). Accordingly, changes in the occurrence of differentiator tag sequences after amplification and sequencing may be indicative of bias in the protocol. Bias may be corrected to provide an accurate representation of the composition of the original MIP pool, e.g., for diagnostic purposes.

According to some aspects, a library of preparative nucleic acid molecules (e.g., MIPs, each nucleic acid in the library having a unique differentiator tag sequence, may be constructed such that the number of nucleic acid molecules in the library is significantly larger than the number prospective target nucleic acid molecules to be captured using the library. This ensures that products of the preparative methods include only unique target:differentiator tag sequence; e.g., in a MIP reaction the capture step would undersample the total population of unique differentiator tag sequences in the MIP library. For example, an experiment utilizing 1 μg of genomic DNA will contain about ~150,000 copies of a diploid genome. For a MIP library, each MIP in the library comprising a randomly produced 12-mer differentiator tag sequence (~1.6 million possible unique differentiator tag sequences), there would be more than 100 unique differentiator tag sequences per genomic copy. For a MIP library, each MIP in the library comprising a randomly produced 15-mer differentiator tag sequence (~1 billion possible unique differentiator tag sequences), there would be more than 7000 unique differentiator tag sequences per genomic copy. Therefore, the probability of the same differentiator tag sequence being incorporated multiple times is incredibly small. Thus, it is to be appreciated that the length of the differentiator tag sequence is to be selected based on the amount of target sequence in a MIP capture reaction and the desired probability for having multiple, independent occurrences of target:differentiator tag sequence combinations.

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FIG. 5 depicts a non-limiting method for genotyping based on target and differentiator tag sequences. Sequencing reads of target and differentiator tags sequences are collapsed to make diploid genotype calls. FIG. 6 depicts non-limiting results of a simulation of a MIP capture reaction in which MIP probes, each having a differentiator tag sequence of 15 nucleotides, are combined with 10000 target sequence copies (e.g., genome equivalents). In this simulated reaction, the probability of capturing one or more copies of a target sequence having the same differentiator tag sequence is 0.05. The Y axis reflects the number of observations. The X axis reflects the number of independent occurrences of target:differentiator tag combinations. FIG. 7 depicts a non-limiting graph of sequencing coverage, which can help ensure that alleles are sampled to sufficient depth (e.g., either 10x or 20x minimum sampling per allele, assuming 1000 targets). In this non-limiting example, the X axis is total per-target coverage required, and the Y axis is the probability that a given total coverage will result in at least 10x or 20x coverage for each allele.

The skilled artisan will appreciate that as part of a MIP library preparation process, adapters may be ligated onto the ends of the molecules of interest. Adapters often contain PCR primer sites (for amplification or emulsion PCR) and/or sequencing primer sites. In addition, barcodes may be included, for example, to uniquely identify individual samples (e.g., patient samples) that may be mixed together. (See, e.g., USPTO Publication Number US 2007/0020640 A1 (McCloskey et al.)

The actual incorporation of the random differentiator tag sequences can be performed through various methods known in the art. For example, nucleic acids comprising differentiator tag sequences may be incorporated by ligation. This is a flexible method, because molecules having differentiator tag sequence can be ligated to any blunt-ended nucleic acids. The sequencing primers must be incorporated subsequently such that they sequence both the differentiator tag sequence and the target sequence. Alternatively, the sequencing adaptors can be synthesized with the random differentiator tag sequences at their 3' end (as degenerate bases), so that only one ligation must be performed. Another method is to incorporate the differentiator tag sequence into a PCR primer, such that the primer structure is arranged with the common adaptor sequence followed by the random differentiator tag sequence followed by the PCR priming sequence (in 5' to 3' order). A differentiator tag sequence and adaptor sequence (which may contain the sequencing primer site) are incorporated as tags. Another

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method to incorporate the differentiator tag sequences is to synthesize them into a padlock probe prior to performing a gene capture reaction. The differentiator tag sequence is incorporated 3' to the targeting arm but 5' to the amplification primer that will be used downstream in the protocol. Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer. This allows the differentiator tag sequence to be incorporated directly at the cDNA level.

In some embodiments, at the incorporation step, the distribution of differentiator tag sequences can be assumed to be uniform. In this case, bias in any part of the protocol would change the uniformity of this distribution, which can be observed after sequencing. This allows the differentiator tag sequence to be used in any preparative process where the ultimate output is sequencing of many molecules in parallel.

Differentiator tag sequences may be incorporated into probes (e.g., MIPs) of a plurality when they are synthesized on-chip in parallel, such that degeneracy of the incorporated nucleotides is sufficient to ensure near-uniform distribution in the plurality of probes. It is to be appreciated that amplification of a pool of unique differentiator tag sequences may itself introduce bias in the initial pool. However, in most practical cases, the scale of synthesis (e.g., by column synthesis, chip based synthesis, etc.) is large enough that amplification of an initial pool of differentiator tag sequences is not necessary. By avoiding amplification or selection steps on the pool of unique differentiator tag sequences, potential bias may be minimized.

One example of the use of the differentiator tag sequences is in genome re-sequencing. Considering that the raw accuracy of most next-generation sequencing instruments is relatively low, it is crucial to oversample the genomic loci of interest. Furthermore, since there are two alleles at every locus, it is important to sample enough to ensure that both alleles have been observed a sufficient number of times to determine with a sufficient degree of statistical confidence whether the sample is homozygous or heterozygous. Indeed, the sequencing is performed to sample the composition of molecules in the originating sample. However, after multiple reads have been collected for a given locus, it is possible that due to bias (e.g., caused by PCR amplification steps), a large fraction of the reads are derived from a single originating molecule. This would skew the population of target sequences observed, and would affect the outcome of the genotype call. For example, it is possible that a locus that is heterozygous is called as

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homozygous, because there are only a few observations of the second allele out of many observations of that locus. However, if information is available on differentiator tag sequences, this situation could be averted, because the over-represented allele would be seen to also have an over-represented differentiator tag sequence (i.e., the sequences with the overrepresented differentiator tag sequence all originated from the same single molecule). Therefore, the sequences and corresponding distribution of differentiator tag sequences can be used as an additional input to the genotype-calling algorithm to significantly improve the accuracy and confidence of the genotype calls.

In some aspects, the disclosure provides methods for analyzing a plurality of target sequences which are genetic loci or portions of genetic loci (e.g., a genetic locus of Table 1). The genetic loci may be analyzed by sequencing to obtain a genotype at one or more polymorphisms (e.g., SNPs). Exemplary polymorphisms are disclosed in Table 2. The skilled artisan will appreciate that other polymorphisms are known in the art and may be identified, for example, by querying the Entrez Single Nucleotide Polymorphism database, for example, by searching with a GeneID from Table 1.

Table 1: Target Nucleic Acids

Gene name	Gene ID	Description	Gene aliases	OMIM	RefSeqGene	Chromosome map position
CYP21A2	1589	cytochrome P450, family 21, subfamily A, polypeptide 2	CAH1; CPS1; CA21H; CYP21; CYP21B; P450c21B; MGC150536; MGC150537; CYP21A2	201910	NG_008337.1	6p21.3
ABCC8	6833	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	HI; SUR; HHF1; MRP8; PHHI; SUR1; ABC36; HRINS; TNDM2; ABCC8	600509	NG_008867.1	11p15.1
ATRX	546	alpha thalassemia/mental retardation syndrome X-linked (RAD54 homolog, S. cerevisiae)	SHS; XH2; XNP; ATR2; SFM1; RAD54; MRXHF1; RAD54L; ZNF-HX; MGC2094; ATRX	300032	NG_008838.1	Xq13.1-q21.1
ARSA	410	arylsulfatase A	MLD; ARSA	607574	NG_009260.1	22q13.31-qter; 22q13.33
PSAP	5660	Prosaposin	GLBA; SAP1; FLJ00245; MGC110993; PSAP	176801	NG_008835.1	10q21-q22
BTD	686	Biotinidase	BTD	609019	NG_008019.1	3p25

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Gene name	Gene ID	Description	Gene aliases	OMIM	RefSeqGene	Chromosome map position
HLCS	3141	holocarboxylase synthetase (biotin-(proprionyl-Coenzyme A-carboxylase (ATP-hydrolysing)) ligase)	HCS; HLCS	609018	NC_000021.7	21q22.1; 21q22.13
BLM	641	Bloom syndrome, RecQ helicase-like	BS; RECQ2; RECQL2; RECQL3; MGC126616; MGC131618; MGC131620; BLM	604610	NG_007272.1	15q26.1
ASPA	443	aspartoacylase (Canavan disease)	ASP; ACY2; ASPA	608034	NG_008399.1	17pter-p13
CFTR	1080	cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)	CF; MRP7; ABC35; ABCC7; CFTR/MRP; TNR-CFTR; dJ760C5.1; CFTR	602421	NC_000007.12	7q31.2
ASS1	445	argininosuccinate synthetase 1	ASS; CTLN1; ASS1	603470	NG_011542.1	9q34.1
MMACHC	25974	methylmalonic aciduria (cobalamin deficiency) cblC type, with homocystinuria	cblC; FLJ25671; DKFZp564I122; RP11-291L19.3; MMACHC	609831	NC_000001.9	1p34.1
IKBKAP	8518	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	FD; DYS; ELP1; IKAP; IKI3; TOT1; FLJ12497; DKFZp781H1425; IKBKAP	603722	NG_008788.1	9q31
FANCC	2176	Fanconi anemia, complementation group C	FA3; FAC; FACC; FLJ14675; FANCC	227645	NG_011707.1	9q22.3
GALK1	2584	galactokinase 1	GK1; GALK; GALK1	604313	NG_008079.1	17q24
GALT	2592	galactose-1-phosphate uridylyltransferase	GALT	606999	NC_000009.10	9p13
GALE	2582	UDP-galactose-4-epimerase	SDR1E1; FLJ95174; FLJ97302; GALE	606953	NG_007068.1	1p36-p35
GBA	2629	glucosidase, beta; acid (includes glucosylceramidase)	GCB; GBA1; GLUC; GBA	606463	NG_009783.1	1q21
GJB2	2706	gap junction protein, beta 2, 26kDa	HID; KID; PPK; CX26; DFNA3; DFNB1; NSRD1; DFNA3A; DFNB1A; GJB2	121011	NG_008358.1	13q11-q12
GCDH	2639	glutaryl-Coenzyme A dehydrogenase	GCD; ACAD5; GCDH	608801	NG_009292.1	19p13.2
G6PC	2538	glucose-6-phosphatase, catalytic subunit	G6PT; GSD1; GSD1a; MGC163350; G6PC	232200	NG_011808.1	17q21
HBB	3043	hemoglobin, beta	CD113t-C; beta-globin; HBB	141900	NG_000007.3	11p15.5

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Gene name	Gene ID	Description	Gene aliases	OMIM	RefSeqGene	Chromosome map position
BCKDHA	593	branched chain keto acid dehydrogenase E1, alpha polypeptide	MSU; MSUD1; OVD1A; BCKDE1A; FLJ45695; BCKDHA	608348	NC_000019.8	19q13.1-q13.2
BCKDHB	594	branched chain keto acid dehydrogenase E1, beta polypeptide	E1B; FLJ17880; dJ279A18.1; BCKDHB	248611	NG_009775.1	6q13-q15
DBT	1629	dihydrolipoamide branched chain transacylase E2	E2; E2B; BCATE2; MGC9061; DBT	248610	NG_011852.1	1p31
DLD	1738	dihydrolipoamide dehydrogenase	E3; LAD; DLDH; GCSL; PHE3; DLD	238331	NG_008045.1	7q31-q32
ACADM	34	acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain	MCAD; ACAD1; MCADH; FLJ18227; FLJ93013; FLJ99884; ACADM	607008	NG_007045.1	1p31
MMAA	166785	methylmalonic aciduria (cobalamin deficiency) cblA type	cblA; MGC120010; MGC120011; MGC120012; MGC120013; MMAA	607481	NG_007536.1	4q31.22
MMAB	326625	methylmalonic aciduria (cobalamin deficiency) cblB type	ATR; cblB; MGC20496; MMAB	607568	NG_007096.1	12q24
MUT	4594	methylmalonyl Coenzyme A mutase	MCM; MUT	609058	NG_007100.1	6p12.3
MCOLN1	57192	mucolipin 1	ML4; MLIV; MST080; TRPML1; MSTP080; TRP-ML1; TRPM-L1; MCOLN1	605248	NC_000019.8	19p13.3-p13.2
ACTA1	58	actin, alpha 1, skeletal muscle	ACTA; ASMA; CFTD; MPFD; NEM1; NEM2; NEM3; CFTD1; CFTDM; ACTA1	102610	NG_006672.1	1q42.13
TPM3	7170	tropomyosin 3	TM3; TRK; NEM1; TM-5; TM30; TM30nm; TPMsk3; hscp30; MGC3261; FLJ41118; MGC14582; MGC72094; OK/SW-cl.5; TPM3	191030	NG_008621.1	1q21.2
TNNT1	7138	troponin T type 1 (skeletal, slow)	ANM; TNT; STNT; TNTS; FLJ98147; MGC104241; TNNT1	191041	NG_011829.1	19q13.4
NEB	4703	nebulin	NEM2; NEB177D; FLJ11505; FLJ36536; FLJ39568; FLJ39584; DKFZp686C1456; NEB	161650	NG_009382.1	2q22
SMPD1	6609	sphingomyelin phosphodiesterase 1, acid lysosomal	ASM; NPD; SMPD1	607608	NG_011780.1	11p15.4-p15.1
GLDC	2731	glycine dehydrogenase (decarboxylating)	GCE; NKH; GCSP; HYGN1; MGC138198; MGC138200; GLDC	238300	NC_000009.10	9p22

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Gene name	Gene ID	Description	Gene aliases	OMIM	RefSeqGene	Chromosome map position
GCSH	2653	glycine cleavage system protein H (aminomethyl carrier)	GCE; NKH; GCSH	238330	NC_000016.8	16q23.2
AMT	275	aminomethyltransferase	GCE; NKH; GCST; AMT	238310	NC_000003.10	3p21.2-p21.1
OTC	5009	ornithine carbamoyltransferase	OCTD; MGC129967; MGC129968; MGC138856; OTC	300461	NG_008471.1	Xp21.1
PAH	5053	phenylalanine hydroxylase	PH; PKU; PKU1; PAH	612349	NG_008690.1	12q22-q24.2
DHPR	5860	quinoid dihydropteridine reductase	DHPR; PKU2; SDR33C1; FLJ42391; QDPR	612676	NG_008763.1	4p15.31
PTS	5805	6-pyruvoyltetrahydropterin synthase	PTPS; FLJ97081; PTS	261640	NG_008743.1	11q22.3-q23.3
PCCA	5095	propionyl Coenzyme A carboxylase, alpha polypeptide	PCCA	232000	NG_008768.1	13q32
PCCB	5096	propionyl Coenzyme A carboxylase, beta polypeptide	DKFZp451E113; PCCB	232050	NG_008939.1	3q21-q22
ACADS	35	acyl-Coenzyme A dehydrogenase, C-2 to C-3 short chain	SCAD; ACAD3; ACADS	606885	NG_007991.1	12q22-qter
DHCR7	1717	7-dehydrocholesterol reductase	SLOS; DHCR7	602858	NC_000011.8	11q13.2-q13.5
SMN1	6606	survival of motor neuron 1, telomeric	SMA; SMN; SMA1; SMA2; SMA3; SMA4; SMA@; SMNT; BCD541; T-BCD541; SMN1	600354	NG_008691.1	5q13
HEXA	3073	hexosaminidase A (alpha polypeptide)	TSD; MGC99608; HEXA	606869	NG_009017.1	15q23-q24
MYO7A	4647	myosin VIIA	DFNB2; MYU7A; NSRD2; USH1B; DFNA11; MYOVIIA; MYO7A	276903	NG_009086.1	11q13.5
USH1C	10083	Usher syndrome 1C (autosomal recessive, severe)	PDZ73; AIE-75; DFNB18; PDZ-45; PDZ-73; NY-CO-37; NY-CO-38; ush1cpst; PDZ-73/NY-CO-38; USH1C	605242	NC_000011.8	11p15.1-p14
CDH23	64072	cadherin-like 23	USH1D; DFNB12; FLJ00233; FLJ36499; KIAA1774; KIAA1812; MGC102761; DKFZp434P2350; CDH23	605516	NG_008835.1	10q21-q22
PCDH15	65217	protocadherin 15	USH1F; DFNB23; DKFZp667A1711; PCDH15	605514	NG_009191.1	10q21.1

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Gene name	Gene ID	Description	Gene aliases	OMIM	RefSeqGene	Chromosome map position
SANS	124590	Usher syndrome 1G (autosomal recessive)	SANS; ANKS4A; FLJ33924; USH1G	607696	NG_007882.1	17q25.1
ARX	170302	aristaless related homeobox	ISSX; PRTS; MRX29; MRX32; MRX33; MRX36; MRX38; MRX43; MRX54; MRX76; MRX87; MRXS1; ARX	300382	NG_008281.1	Xp21
OPHN1	4983	oligophrenin 1	OPN1; MRX60; OPHN1	300127	NG_008960.1	Xq12
JARID1C	8242	lysine (K)-specific demethylase 5C	MRXJ; SMCX; MRXSJ; XE169; JARID1C; DXS1272E; KDM5C	314690	NG_008085.1	Xp11.22-p11.21
FTSJ1	24140	FtsJ homolog 1 (E. coli)	JM23; MRX9; SPB1; TRM7; CDLIV; MRX44; FTSJ1	300499	NG_008879.1	Xp11.23
SLC6A8	6535	solute carrier family 6 (neurotransmitter transporter, creatine), member 8	CRT; CT1; CRTR; MGC87396; SLC6A8	300036	NC_000023.9	Xq28
DLG3	1741	discs, large homolog 3 (Drosophila)	MRX; MRX90; NEDLG; NE-Dlg; SAP102; SAP-102; KIAA1232; DLG3	300189	NC_000023.9	Xq13.1
TM4SF2	7102	tetraspanin 7	A15; MXS1; CD231; MRX58; CCG-B7; TM4SF2; TALLA-1; TM4SF2b; DXS1692E; TSPAN7	300096	NG_009160.1	Xp11.4
ZNF41	7592	zinc finger protein 41	MRX89; MGC8941; ZNF41	314995	NG_008238.1	Xp11.23
FACL4	2182	acyl-CoA synthetase long-chain family member 4	ACS4; FACL4; LACS4; MRX63; MRX68; ACSL4	300157	NG_008053.1	Xq22.3-q23
PQBP1	10084	polyglutamine binding protein 1	SHS; MRX55; MRXS3; MRXS8; NPW38; RENS1; PQBP1	300463	NC_000023.9	Xp11.23
PEX1	5189	peroxisomal biogenesis factor 1	ZWS1; PEX1	602136	NG_008341.1	7q21.2
PXMP3	5828	peroxisomal membrane protein 3, 35kDa	PAF1; PEX2; PMP3; PAF-1; PMP35; RNF72; PXMP3	170993	NG_008371.1	8q21.1
PEX6	5190	peroxisomal biogenesis factor 6	PAF2; PAF-2; PXAAA1; PEX6	601498	NG_008370.1	6p21.1
PEX10	5192	peroxisomal biogenesis factor 10	NALD; RNF69; MGC1998; PEX10	602859	NG_008342.1	1p36.32
PEX12	5193	peroxisomal biogenesis factor 12	PAF-3; PEX12	601758	NG_008447.1	17q12
PEX5	5830	peroxisomal biogenesis factor 5	PXR1; PTS1R; PTS1-BP; FLJ50634; FLJ50721; FLJ51948; PEX5	600414	NG_008448.1	12p13.31
PEX26	55670	peroxisomal biogenesis factor 26	FLJ20695; PEX26M1T; Pex26pM1T; PEX26	608666	NG_008339.1	22q11.21

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The mutations listed in Table 2 are documented polymorphisms in several disease-associated genes (CFTR is mutated in cystic fibrosis, GBA is mutated in Gaucher disease, ASPA is mutated in Canavan disease, HEXA is mutated in Tay Sachs disease). The polymorphisms are of several types: insertion/deletion polymorphisms which will cause frameshifts (and thus generally interrupt protein function) unless the insertion/deletion length is a multiple of 3bp, and substitutions which can alter the amino acid sequence of the protein and in some cases cause complete inactivation by introduction of a stop codon.

Table 2: Non-limiting examples of polymorphisms

Gene name	GeneID	SNP ID	Mutation	SEQ ID NO:
CFTR	1080	rs63500661	TCACATCACCAAGTTAAAAAAAAAAA[A/G]G GGGCGGGGGGGCAGAATGAAAATT	1
CFTR	1080	rs63107760	AAACAAGGATGAATTAAGTTTTTTTT[-/T]AAAAAAGAAACATTTGGTAAGGGGA	2
CFTR	1080	rs62469443	ATCACCAAGTTAAAAAAAAAAAAGGG[A/G]C GGGGGGGCAGAATGAAAATTGCAT	3
CFTR	1080	rs62469442	CTATTGAACCAGAACCAAACAGGAAT[A/G]C CATAGCATTTTGTAAACTAAACTG	4
CFTR	1080	rs62469441	CAGGAGTTCAAGACCAGCCTACTAAA[A/C]C ACACACACACACACACACACACAC	5
CFTR	1080	rs62469439	GATTAAATAATAGTGTTTATGTACCC[C/G]GC TTATAGGAGAAGAGGGTGTGTGT	6
CFTR	1080	rs62469438	ATTGTTATCTTTTCATATAAGGTAAC[A/T]GA GGCCCAGAGAGATTAAATAACAT	7
CFTR	1080	rs62469437	TAATTTTAATTAAGTAAATTTAATTG[A/G]TA GATAAATAAGTAGATAAAAAATA	8
CFTR	1080	rs62469436	GTATAAAAAAAAAAAAAAAAAAAGTT[A/T]G AATGTTTTCTTGCATTCAGAGCCT	9
CFTR	1080	rs62469435	ATACTAAAAATTTAAAGTTCTCTTGC[A/G]AT ATATTTTCTTAATATCTTACATC	10
CFTR	1080	rs62469434	TGCTGGGATTACAGGCGTGAGCCACC[A/G]C GCCTGGCCTGATGGGACATATTTT	11
CFTR	1080	rs62469433	CTACAATATAAGTATAGTATTGCAAA[A/C]CC ATCAGGAAGGGTGTTAACTATTT	12
CFTR	1080	rs61763210	GTTGTCTCCAAACTTTTTTTCAGGTG[-/AGA]AGGTGGCCAACCGAGCTTCGGAAAG	13
CFTR	1080	rs61720488	TTTTTTCATAAAAGATTATATAAAGG[A/C]TA TTGCTTTTGAATCACAAACACTA	14
CFTR	1080	rs61481156	ATCTAGTGAGCAGTCAGGAAAGAGAA[C/T]T TCCAGATCCTGGAAATCAGGGTTA	15
CFTR	1080	rs61443875	TAGAGTATAAAAAAAAAAAAAAAAA[-/A]GTTTGAATGTTTTCTTGCATTCAGA	16

CFTR	1080	rs61312222	TGCAAATGCCAACTATCAAAGATATT[C/G]GAGTATACTGTCAATAAACTTCATA	17
CFTR	1080	rs61159372	TCCTCAACAGTTAGAAACAATATTTT[C/G]AGTGATTTCCCATGCCAACTTTACT	18
CFTR	1080	rs61094145	TTTTTGGTATTGTTGTTAAATAAGTG[A/G]GAATTCAATACAGTATAATGTCTGT	19
CFTR	1080	rs61086387	CTTGAAATCGGATATATATATATATA[-/TGTATATATATATATATATATATATATATACATATATATATATA]GTATTATCCCTGTTTTCACAGTTTT	20
CFTR	1080	rs60996744	AGAGGGGCTGTGAAGGACACCAAGGA[A/G]GAGACTAAGAGCCAGGAGGGAAAAC	21
CFTR	1080	rs60960860	TAGAGTTTATTAGCTTTTACTACTCT[A/G]CTTAGTTACTTTGTGTTACAGAATA	22
CFTR	1080	rs60923902	ACTAGTGATGATGAGCTTCTTTTCAT[-/AT]GTTTGTTGGCTGCATAAATGTCTTC	23
CFTR	1080	rs60912824	GCAGAGAAAAGAGGGGCTGTGAAGGA[C/G]ACCAAGGAGGAGACTAAGAGCCAGG	24
CFTR	1080	rs60887846	TTCAGAGGTCTACCACTGGTGCATAC[G/T]CTAATCACAGTGTCGAAAATTTTAC	25
CFTR	1080	rs60793174	AAGAAAGAGCAAAAGAGGGCAAACTT[C/T]TCATACATTTTTGATGTCGAAACCA	26
CFTR	1080	rs60788575	CCTAAAGTTTAAAAAGAAAAAAAAAA[-/A]GGAAGAAGGAATTAAAAATCCAAAG	27
CFTR	1080	rs60760741	GTGTGTGTGTGTATATATATATATAT[A/T]TATATATTTTTTTTTTCCTGAGCCA	28
CFTR	1080	rs60456599	AAACTGTTGATGTTTTCATTTATTTA[C/G]ATCATTGGAAAACTTTAGATTCTAG	29
CFTR	1080	rs60363249	TTTATCCATTCTTAACCAGAACAGAC[A/G]TTTTTTCAGAGCTGGTCCAGGAAAA	30
CFTR	1080	rs60355115	TTGAAATCGGATATATATATATATAT[A/G]TATATATATATATATATATATATAT	31
CFTR	1080	rs60308689	TAGTTTTTTATTTCCTCATATTATTT[-/T]CAGTGGCTTTTTCTTCCACATCTTT	32
CFTR	1080	rs60271242	ACATAGTTCTCAGTGGTACAACTACA[A/G]GTGATTTCTCTTTTCTTATTTCTGG	33
CFTR	1080	rs60010318	AGAGCAATGGCATCCCTTGTCTTGTG[C/T]TATACAGGATGCAGCAATTTATAGG	34
CFTR	1080	rs59961323	TTCTGTCTACATAAGATGTCATACTA[A/G]ATTATCTTTTCCAGCATGCATTCAG	35
CFTR	1080	rs59961270	CAGGGTGGCATGTTAGGCAGTGCTTA[A/G]AATAAATGAGTTGGTTATACAAGTA	36
CFTR	1080	rs59837506	AGGACACACACACACACACACACACA[-/CA]TGCACACACATTTAAATAGATGCAT	37
CFTR	1080	rs59572090	TAAAAAATTGGTATAATGAAATTGCA[C/T]TTGTAGTCTTTGGACATTTAAATCC	38
CFTR	1080	rs59548252	TTTCAATACTTAAGAGGTACGCAGAG[A/G]AAAGAGGGGCTGTGAAGGACACCAA	39
CFTR	1080	rs59519859	CAGCAATGAATATTTTGAGGCTGAGG[C/T]GCTGAGGGGTAAAATTGCAGCCTGG	40
CFTR	1080	rs59509837	TTATGGTTTATATTTTTGTGTCTTCT[-/CTTT]AACACATCTTTTCTAGCAGAATTCA	41

CFTR	1080	rs59417037	GTATTTTAGTTTTTTTTTTTTGTTTG[-/T]TTTGTTTTGTTTTGTTTTGTTTTTG	42
CFTR	1080	rs59159458	TGGGTGACTCCATTTTTACTTTTAGT[C/T]TGGTCTGTTGAGGCCTCGTGAGAGA	43
CFTR	1080	rs59048119	TATTTTCATGTATTTTAGTTTTTTTTT[-/TTTT]GTTTGTTTTGTTTTGTTTTGTTTTG	44
CFTR	1080	rs58970500	GTGTGTGTGTATATATATATATATAT[A/T]TATATTTTTTTTTTCCTGAGCCAAA	45
CFTR	1080	rs58942292	AACCTATTAGCATGTCTGGCAGAAAA[-/A]TAGATACTTAATAAATTTCTTAAAT	46
CFTR	1080	rs58917054	GAGGCTTAGACAGTTTAAGTAACTCA[A/G]GCATGGTTACACAACTAGCTAGGGC	47
CFTR	1080	rs58837484	GTGTGAGTATTATGAGACCATATGTT[A/G]GGAGATTTTATTTGGTATTGAGGAT	48
CFTR	1080	rs58829491	GAAACCCCACCCCTTCTATAGTTTTC[C/T]CTTTAATATTTACAATGGAACCATT	49
CFTR	1080	rs58805195	CATATATATATAGTGTGTGTGTGTGT[A/G]TATATATATATATATATATTTTT	50
GBA	2629	rs60866785	CGAGCGAGAGAGAGAGAGAGAGAGAG[-/AG]GAGCCGGCGCGAGAACTACGCATGC	51
GBA	2629	rs60239603	GGCAGGTAATATCTAGTACCTTACTT[A/T]TATTTCCTGAGCACATTCTACATTT	52
GBA	2629	rs56310840	GGCCAGGAATGGGAGTGCTTAGGTGC[A/G]GAGGTGGCACTGTTCCCGCAGCTGC	53
GBA	2629	rs41264927	TGAAAACTCCATCCCCTCAGGGTCAT[C/T]AGATGAAGAGAAGACCACAGGGGTT	54
GBA	2629	rs41264925	TGTAGGTAAGGGTCACATGTGGGAGA[C/G]GCAGCTGTGGGTAGGTCAGCCCTGT	55
GBA	2629	rs36024691	CCAAGAAGGCGCCATTACACTCCAGC[-/C]TGGGCGACAGGGCGAGACTCCCTCA	56
GBA	2629	rs36024092	TGCCACACCCAGCTAATTTGTGTGTG[-/G]TATGTGTGTGTATGTATGTGTGTGT	57
GBA	2629	rs35682967	GTTCCTCCAGTAATTTTTTTTTTTTT[-/T]GGTTTTGAGACAGAGTCTTGCCCTG	58
GBA	2629	rs35033592	ATCATGCCCAGATAATTTTTTTTTTT[-/T]GTATTTTAGTAGACACAGGGTTTCA	59
GBA	2629	rs34732744	CGAGCGAGAGAGAGAGAGAGAGAGAG[-/AG]GAGCCGGCGCGAGAACTACGCATGC	60
GBA	2629	rs34620635	CCTGTGAGGGGCACATTCCTTAGTAG[-/C]TAAGGAGTTGGGGGTGTGAAGATCC	61
GBA	2629	rs34302637	ACAGGCTACTGGCTGGGCCCAGGCAA[-/A]GGGGGCCTTGGCAGGAAAAGTTCCT	62
GBA	2629	rs33949225	GCGAGAGAGAGAGAGAGAGAGAGAGG[-/AG]AGCCGGCGCGAGAACTACGCATGCG	63
GBA	2629	rs28678003	AAGAAGAAAAATAAAAAGAAAGTGGG[C/T]CAGACCGAGAGAACAGGAAGCCTGA	64
GBA	2629	rs28559737	AAGGACAAAGGCAAAGAGACAAAGGC[G/T]CAACACTGGGGGTCCCCAGAGAGTG	65
GBA	2629	rs28373017	TACCTAGTCACTTCCTGCCTCCATGG[C/T]GCAAAAGGGGATGGGTGTGCCTCTT	66
GBA	2629	rs12752133	CTCTTCCGAGGTTCCACCCTGAACAC[C/T]TTCCTGCTCCCTCGTGGTGTAGAGT	67

GBA	2629	rs12747811	TTCTGACTGGCAACCAGCCCCACTCT[C/T]TG GGAGCCCTCAGGAATGAACTTGC	68
GBA	2629	rs12743554	gctcagcctcccaggctggagtgcag[A/T]ggcgcgatctcggctcac cgcaacc	69
GBA	2629	rs12041778	CATGAACCACATCAAATGAGATTTAG[C/T]GG GAGTGGCACACACAGTCATGACC	70
GBA	2629	rs12034326	AAGCAGCCCTGGGGAGTCGGGGCGGG[A/G]C CTGGATTGGAAAAGAGACGGTCAC	71
GBA	2629	rs11558184	CTCCAAGTTCTGGGAGCAGAGTGTGC[A/G]G CTAGGCTCCTGGGATCGAGGGATG	72
GBA	2629	rs11430678	GTTCCTCCAGTAAttttttttttt[- /G/T]gttttgagacagagtcttgccctgt	73
GBA	2629	rs11264345	CTAGTACCTTACTTCCCTCAAGTTCA[A/T]TC ATCTCACAGATATTTCCTGAGCA	74
GBA	2629	rs10908459	aattagccgtgcgtggtggcgggtgc[C/T]tgtaatcccacgtactttgg gaggct	75
GBA	2629	rs10796940	CCATGGCCAGCCGGGGAGGGGACGGG[A/C]A CACACAGACCCACACAGAGACTCA	76
GBA	2629	rs10668496	agcgagagagagagagagagagagag[- /AG]gagCCGGCGCGAGAACTACGCATGC	77
GBA	2629	rs7416991	CGTAGCAGTTAGCAGATGATAGGCGG[C/G/T] GAAATCTTATTTCACAGGGCATTAA	78
GBA	2629	rs4024049	CTGGCCCTGGTGACAGTGGGGCTGTG[C/T]GT GGGGCCAGAGCCTTCTCAGAGGT	79
GBA	2629	rs4024048	CAGATACTGGCCCTGGTGACAGTGGG[A/G]C TGTGCGTGGGGCCAGAGCCTTCTC	80
GBA	2629	rs4024047	GACAGATACTGGCCCTGGTGACAGTG[G/T]G GCTGTGCGTGGGGCCAGAGCCTTC	81
GBA	2629	rs3841430	GGCTCctctctctctctctctctc[- /TC]gctcgctctctcgctctctcgctct	82
GBA	2629	rs3754485	GTTTCAGACCAGCCTGGCCAACATAG[C/T]GA AACCCCATCTCTACTAAAAATAA	83
GBA	2629	rs3205619	AGTGGGCGATTGGATGGAGCTGAGTA[C/T]G GGGCCCATCCAGGCTAATCACACC	84
GBA	2629	rs2990227	CCGGGCTCCGTGAATGTTTGTCACAT[C/G]TC TGAAGAACGTATGAATTACATAA	85
GBA	2629	rs2990226	GAATCCCAACCCCGACGCTCGTCGCC[C/G]G GCTCCGTGAATGTTTGTCACATGT	86
GBA	2629	rs2990225	GCGAATCCCAACCCCGACGCTCGTCG[C/T]CG GGCTCCGTGAATGTTTGTCACAT	87
GBA	2629	rs2990224	TGGGCAGAAGTCAGGGTCCAAAGAAA[G/T]G GCAAAGAAAAGTGTcagtggctca	88
ASPA	443	rs63751297	TAAGAAAGACGTTTTTGATTTTTTTC[A/G]GA CTTCTCTGGCTCCACTACCCTGC	89
ASPA	443	rs62071301	CTGATTCCTGGCCAGGAGCGGTGGCT[C/T]AC GCCTGTAATCCCAGCGCTTTGGG	90
ASPA	443	rs62071300	TAAAAATGCTGATTCCTGGCCAGGAG[C/T]GG TGGCTCACGCCTGTAATCCCAGC	91
ASPA	443	rs62071299	TTTAAAAATGCTGATTCCTGGCCAGG[A/C]GC GGTGGCTCACGCCTGTAATCCCA	92
ASPA	443	rs62071297	CAAGACCTGTCAAAGATCTGAGAAAT[A/T]TT ACCCGACTTACAAGCTAACCATT	93

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ASPA	443	rs61697033	ACTGTAATAAGTGCTGTAAAAGAAAT[A/G]C ACAAAATAATATAGCAGAGGGTAT	94
ASPA	443	rs60743592	CTTGAGGTCAGGAGTTCAAGACCAGT[C/T]TG GGCAACATGGGGAAAACCTTGTC	95
ASPA	443	rs60666840	AGGTTGCAGTGAGCCGAGATCATGCC[A/G]TT GCACTCCAGCCGGGGCAACAAAA	96
ASPA	443	rs60147514	ACAAGTGTCTTGAAATTATCTGTGAT[C/T]TG CTATAGAGCAATACTTTTGTAAA	97
ASPA	443	rs59930743	GTGGGTATATGCAGCTCTATGCACTA[C/T]CT GCTCATTTATTTGGTAAATCTAA	98
ASPA	443	rs59690349	TGTGTGTGTGTGCGTGTGTGTGTGTG[-/TGTGTGTG]ATCATAAGAGTGGCTGCAGCAA ACT	99
ASPA	443	rs59676360	AGTCTGGAGTGCAATGGTGCAATCTC[A/G]GC TCACTGCAGCCTCCACCTCCGGG	100
ASPA	443	rs59335404	CTCCTAATGGATATTTCCTAAATTTT[G/T]CTG AACAGAATTTAACTTGAGCTGG	101
ASPA	443	rs58879097	ATTTAAAAATGGATTTCTAGAAAAAC[A/G]AT CACATACTTGAATATTTTAGCAA	102
ASPA	443	rs58686774	CTATAAATGGGTAGCATGAGGGATTC[A/G]A GGAGGTGGCTGAAAGAAGCACGTA	103
ASPA	443	rs57511162	AAGAAACCAAGCATAGTAGAGTGTTA[A/G]A AAACCAAAGCAACTAAACAACTGT	104
ASPA	443	rs55859596	CGGGGCTCAGAACTTGTAACAGAAAA[A/T]T AAAATATACTCCACTCAAGGGAAT	105
ASPA	443	rs55742972	TACTACACTTCACGGATACTGTACTT[-/GTACTT]TTTTTCCAAATTGAAGGTTTTTGGC	106
ASPA	443	rs55640436	TTGTTTTTGTTTTTGTTTTTGTTTTT[-/GTTTTTGTTTTT]TGAGATGGAGTCTCGCTCT GTCGCC	107
ASPA	443	rs36225687	TTTGCCTTACTACACTTCACGGATAC[-/TGTACT]TGTACTTTTTTTCCAAATTGAAGGT	108
ASPA	443	rs36051310	GAGGTGGCTGAAAGAAGCACGTATCC[-/C]TGATGGCATGGTTGCGGGTTATATG	109
ASPA	443	rs36034906	GAGAAAAGCAGTTCCTGGAACACCCC[-/C]ACCCCTTAACCCCTTATCTCTGCTT	110
ASPA	443	rs36033666	TTACATATGTATACATGTGCCATGTT[-/T]GGTGTGCCGCACCCATTAACTCGTC	111
ASPA	443	rs35730123	CTTTTTCCAGATTTTTTTTTTTTTTT[-/T]GAGACAGAGTTTCACTCTTGTTGCC	112
ASPA	443	rs35629100	TTTGGAAATCTTAAGCTTTTATTTGG[-/G]TGTCACAGAGAAACAGGATCTGTAT	113
ASPA	443	rs35614631	TACTTTAAGTTTTAGGGTACATGTGC[-/A]CCATGTGCAGGTTTGTTACATATGT	114
ASPA	443	rs35225782	ATTCATGACCAGCCACATAAATGCAC[-/A]GTATTACTTCGCAAGCATGCCAATG	115
ASPA	443	rs35178659	GTGCACTAGAATTAGCTAAAGTGGGG[-/G]AAAAAAAGATGCATTTGATGGTCTA	116
ASPA	443	rs35095578	AACCTCCACCTCCCAGGTTCAAGAGA[-/A]TTCTCCTGCCTCAGCCTCCCAAGTA	117
ASPA	443	rs35002210	CCTCCCTGTGATCCGAAGTAGCAGAC[A/G]TA CTTAACTTCCATGGTGGATTGTT	118

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ASPA	443	rs34744839	AAAACATTATTATATCTAGAAAAAAA[-/A]TGTATCTTAACCATTGTGGGAAGTG	119
ASPA	443	rs34680506	TTGAAGGTAAAATCATAGGGAGTTGG[-/G]AGCTGTCCTCTTGCGCTGAATCAGT	120
ASPA	443	rs34365618	ACTTGTGGCCTTTTTGGAGAGGTTAG[-/CA]ACTCTGAAAACTCTGTCCCTGGACC	121
ASPA	443	rs34275920	GAAGGAGAAAAAGAGAGGAAATAAGT[-/T]AAAATAATAAACACAATTAATAAAG	122
ASPA	443	rs34109510	TGTATACATGTGCCATGTTGGTGTGC[C/T]GCACCCATTAACTCGTCATTTAGCA	123
ASPA	443	rs34054576	TCACCTGTCACCTCCTATAGAACTTT[-/C]CCCTGACCCTCCTCTATAGCATTAA	124
ASPA	443	rs34015272	ATAAATGATCATCATTCACAGTAGGG[-/G]TTTTGTTTTGTTTTTTTTCTGGAAA	125
ASPA	443	rs34002091	ACAGACATATCTACAAACACACTTTT[-/T]CACATATTTGTGTAAGTCATTTATG	126
ASPA	443	rs28940574	AAAGACAACTAAACTAACGCTCAATG[A/C]AAAAAGTATTCGCTGCTGTTTACAT	127
ASPA	443	rs28940279	TACCGTGTACCCCGTGTTTGTGAATG[A/C]GGCCGCATATTACGAAAAGAAAGAA	128
ASPA	443	rs17850703	CAGGGCTGGAGGTAAAACCATTTATT[A/G]CTAACCCCAGAGCAGTGAAGAAGTG	129
ASPA	443	rs17222495	TTCTTCATTGCCTATTGAAGAGAGAG[C/T]GGAATGCTTTGGTTGCCAGATATGG	130
ASPA	443	rs17175228	CACAAGATCTCATTACTCAGGAGCTG[C/T]CCAAGTGTCTAATGTACTTAGTTAA	131
ASPA	443	rs16953074	TTCTGTGTAACATTTCATTTAAGCAA[A/G]GGATTCGGCAAATCAAAAATTGTCA	132
ASPA	443	rs16953070	TAAAACGTATTGAAGGTATTATTGAC[G/T]CTGTTGAAGCAAAGAGAACAAAACA	133
HEXA	3073	rs62022858	ATCTGCTCTTCCAGTTGGATGACAAG[C/T]CTTGCTGTCTAACACCTGCTGCAGA	134
HEXA	3073	rs62022857	CCATTTTTTGTTGTATTTTTTTTTTC[C/T]TGAATACTTTTTATCGCAGTTGGTT	135
HEXA	3073	rs62017872	CCCTGTCTCTAAAAGAAAAAAAAAAA[A/G]AAAAAAAAAGAAAACAAAACCCAA	136
HEXA	3073	rs62017871	AGTGGCTCCAAAAAGGTCATGGAACC[C/T]CTTGAGGATGATGCAAATTGACTCT	137
HEXA	3073	rs61662730	TAAAGTTACTTTTCTTTTATTGACTT[C/T]CCCTTATTTTTTAACCTTATGCTTT	138
HEXA	3073	rs61329913	CAGAGTTAAAAAAAAAAAAAAAAAA[-/A]GGAAGTAGCAGCAACAGCTTGGAAA	139
HEXA	3073	rs60920713	GTTGCCCAGGGTTGAGTGCAGAGGCA[C/T]ATCTTGGCTCACAGCAACCTCTGCC	140
HEXA	3073	rs60783213	AAGGCTTTTTTTTTTTTTTTTTTTT[-/TTTT]GAGACAGAGTCTTGCTGTGTCACCC	141
HEXA	3073	rs60644867	GCCTACATTCTGCAAAGAGGAGGGAA[C/G]ATTCACAGCTCCATACTTGAACCCT	142
HEXA	3073	rs60288568	CCAAAGGAGAATAGCTCTAGGGGAGG[C/G]AGGTGGATGAGTATGCATGGGGGAG	143
HEXA	3073	rs59888548	GACTCCATCTCAAAAAAAAAAAAAA[-/A]TGCAGTCTAATGGCAGAATTAGACT	144

HEXA	3073	rs59733856	TTATTTATTTATTTATTTATTTTTGA[A/G]ACA GGGTCTCTGTTGTCCAGGCTGG	145
HEXA	3073	rs59427837	TTTTGAGGCAGGGTCTCACTCTGTTG[C/T]CC AGGGTTGAGTGCAGAGGCACATC	146
HEXA	3073	rs59171976	CGCCTTGCGAAGGCCCCACAGCTTGC[C/T]TG TGACAAACGTTCATAGGCAAATG	147
HEXA	3073	rs58706602	GGAGGTCTGTACAAAGCACCACCTAC[C/T]TC ATGGGTCAGTTTCCACAGCAGAA	148
HEXA	3073	rs58696963	GAATCTTATAATTCACTGTGTACCTC[- /CCTC]TGTTTCATATTTTCGCAATTGAACT	149
HEXA	3073	rs58610850	AACATAGTATCTAATATAGCTTTACA[C/T]CC AAAGCCAAAATATGAATACACTG	150
HEXA	3073	rs58016062	TTGTTTTGTTTTGTTTGGGGGGGGGG[- /G]TTGTTTTTCTGAGAGGGAGTCTTGC	151
HEXA	3073	rs57733983	CATACCAAAGGGCAGCTGGAGGGATA[C/T]A GACGGAAGTCATGTGGAGAGTGAA	152
HEXA	3073	rs57476645	CAGGTGTGAGCCACCACGACCACCAA[A/T]T TAGCTCTTTTTACTCCTTCCCTTC	153
HEXA	3073	rs56870003	AGTGGTAGCTGATTTTGCTTCTGGAT[A/C]CT TTGCCACCTTCCCACTCTTTAAT	154
HEXA	3073	rs56338339	AAAGACCTGTTTCTTAAAAAAAAAAA[- /AGAAAAAAAAAAA]GAAAGAAAAGAAAAG AAAAAAACAG	155
HEXA	3073	rs55995352	TAAAAAATCTTTCAATGAGGAGATGT[C/T]CC CAGAGCAAGACAGCTGTAGGATG	156
HEXA	3073	rs55860138	AAAAGAAAAAAAAAAAAAAAAAAAA[- /A]GAAAACAAAACCCAAACCCATAAAG	157
HEXA	3073	rs55743646	CCTGTCTCTAAAAGAAAAAAAAAAAA[A/G]A AAAAAAAAGAAAACAAAACCCAAA	158
HEXA	3073	rs55665666	GTTATCATAGAAAAATATCACACTCT[- /GT]CTGTATCCCCACTTCCAGAAACTGT	159
HEXA	3073	rs36106892	CAGGAGCTCATAGAATTACATACAAT[- /C]TTTTTTTTTTTTTTTTTGAGACAGCG	160
HEXA	3073	rs36091525	TTGAGAATCTTATAATTCACTGTGTA[- /CCTC]CCTCTGTTTCATATTTTCGCAATTG	161
HEXA	3073	rs35949555	CCACTACCACAGTGCCTAGAGAACAA[C/T]A TGTGTTTAATAATATTTAAATAAT	162
HEXA	3073	rs35827424	CCCTGTCTCTAAAAGAAAAAAAAAAA[- /A]AAAAAAAAAAGAAAACAAAACCCAA	163
HEXA	3073	rs35729578	CCATTATATCATTCATTTCCCACTCA[- /T]TTTCTTCATTCCAACCAAGATATAT	164
HEXA	3073	rs35649102	TCCGTCTCAAAAAAAAAAAAAAAAAG[- /A]GAAAGGAATTATTCTCATGTATACA	165
HEXA	3073	rs35118677	CTGGGGCAGTTAAAAAGAAAAACAAA[- /C]CCCTGGTCCCTGCCCTTGAGGAGAT	166
HEXA	3073	rs35005352	CTCCAGGGTCCCATTCCAGGACCACA[- /C]GCCTGCTACCTCTGCAGCTCACTCA	167
HEXA	3073	rs34736306	GGATTGACATATACCAGTTAGACGGA[- /T]TTTTTTTTTCCATAAACCAGGCTCA	168
HEXA	3073	rs34607939	ACAAATAATTACTACATATCTACAAC[A/G]TT CCAGATACAGAAGAAATGGCCAA	169

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HEXA	3073	rs34496117	TAAACACACTTGAAACATCATATAAA[-/ATG]ATATTACTACAAGACTTAACCGTAA	170
HEXA	3073	rs34300017	ACACAGGTAATCCATGTTTATTATAG[-/A]AAAATGCCACATTACTCTTTATTGA	171
HEXA	3073	rs34206496	AGTTATCATAGAAAAATATCACACTC[-/TG]TCTGTATCCCCACTTCCAGAAACTG	172
HEXA	3073	rs34110830	AATGAACTTACAGGAAGGTAATATAT[-/G]GGAAATAAACATCTTATTGAATTTA	173
HEXA	3073	rs34093438	GGACCCCTGAAAGGCACAAGACACCC[-/T]TTCAGGTTCACACTTCCTGAAAGCT	174
HEXA	3073	rs34085965	CCACCAATCACCAGAGCCTTCTGCTC[A/G]GGGGTACCTGAGGGAAAACAAGCAA	175
HEXA	3073	rs34004907	AAAGACTGAAAAAACATTCATAACTA[-/T]TTTTCTTGTTATCCTCGGAAATGTC	176
HEXA	3073	rs28942072	TATCTTCATCTTGGAGGAGATGAGGT[C/T]GATTTCACCTGCTGGAAGTCCAACC	177
HEXA	3073	rs28942071	TTGCCTATGAACGTTTGTCACACTTC[C/T]GCTGTGAGTTGCTGAGGCGAGGTGT	178
HEXA	3073	rs28941771	GCTTGCTGTTGGATACATCTCGCCAT[C/T]ACCTGCCACTCTCTAGCATCCTGGA	179
HEXA	3073	rs28941770	CCGGGGCTTGCTGTTGGATACATCTC[G/T]CCATTACCTGCCACTCTCTAGCATC	180

3. Nucleic acid target length evaluation:

In some embodiments, aspects of the invention relate to methods for detecting nucleic acid deletions or insertions in regions containing nucleic acid sequence repeats.

Genomic regions that contain nucleic acid sequence repeats are often the site of genetic instability due to the amplification or contraction of the number of sequence repeats (e.g., the insertion or deletion of one or more units of the repeated sequence). Instability in the length of genomic regions that contain high numbers of repeat sequences has been associated with a number of hereditary and non hereditary diseases and conditions.

For example, "Fragile X syndrome, or Martin-Bell syndrome, is a genetic syndrome which results in a spectrum of characteristic physical, intellectual, emotional and behavioral features which range from severe to mild in manifestation. The syndrome is associated with the expansion of a single trinucleotide gene sequence (CGG) on the X chromosome, and results in a failure to express the FMR-1 protein which is required for normal neural development. There are four generally accepted forms of Fragile X syndrome which relate to the length of the repeated CGG sequence; Normal (29-31 CGG

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repeats), Premutation (55-200 CGG repeats), Full Mutation (more than 200 CGG repeats), and Intermediate or Gray Zone Alleles (40 - 60 repeats)."

Other examples include cancer, which has been associated with microsatellite instability (MSI) involving an increase or decrease in the genomic copy number of nucleic acid repeats at one or more microsatellite loci (e.g., BAT-25 and/or BAT-26). The are currently many sequencing-based assays for determining the number of nucleic acid sequence repeats at a particular locus and identifying the presence of nucleic acid insertions or deletions. However, such techniques are not useful in a high throughput multiplex analysis where the entire length of a region may not be sequenced.

In contrast, in some embodiments, aspects of the invention relate to detecting the presence of an insertion or deletion at a genomic locus without requiring the locus to be sequenced (or without requiring the entire locus to be sequenced). Aspects of the invention are particularly useful for detecting an insertion or deletion in a nucleic acid region that contains high levels of sequence repeats. The presence of sequence repeats at a genetic locus is often associated with relatively high levels of polymorphism in a population due to insertions or deletions of one or more of the sequence repeats at the locus. The polymorphisms can be associated with diseases or predisposition to diseases (e.g., certain polymorphic alleles are recessive alleles associated with a disease or condition). However, the presence of sequence repeats often complicates the analysis of a genetic locus and increases the risk of errors when using sequencing techniques to determine the precise sequence and number of repeats at that locus.

In some embodiments, aspects of the invention relate to determining the size of a genetic locus by evaluating the capture frequency of a portion of that locus suspected of containing an insertion or deletion (e.g., due to the presence of sequence repeats) using a nucleic acid capture technique (e.g., a nucleic acid sequence capture technique based on molecular inversion probe technology). According to aspects of the invention, a statistically significant difference in capture efficiency for a genetic locus of interest in different biological samples (e.g., from different subjects) is indicative of different relative lengths in those samples. It should be appreciated that the length differences may be at one or both alleles of the genetic locus. Accordingly, aspects of the invention may be used to identify polymorphisms regardless of whether biological samples being interrogated at heterozygous or homozygous for the polymorphisms. According to

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aspects of the invention, subjects that contain one or more loci with an insertion or deletion can be identified by analyzing capture efficiencies for nucleic acids obtained from one or more biological samples using appropriate controls (e.g., capture efficiencies for known nucleic acid sizes, capture efficiencies for other regions that are not suspected of containing an insertion or deletion in the biological sample(s), or predetermined reference capture efficiencies, or any combination thereof. However, it should be appreciated that aspects of the invention are not limited by the nature or presence of the control. In some embodiments, if a statistically significant variation in capture efficiency is detected, a subject may be identified as being at risk for a disease or condition associated with insertions or deletions at that genetic locus. In some embodiments, the subject may be analyzed in greater detail in order to determine the precise nature of the insertion or deletion and whether the subject is heterozygous or homozygous for one or more insertions or deletions. For example, gel electrophoresis of an amplification (e.g., PCR) product of the locus, or Southern blotting, or any combination thereof can be used as an orthogonal approach to verify the length of the locus. In some embodiments, a more exhaustive and detailed sequence analysis of the locus can be performed to identify the number and types of insertions and deletions. However, other techniques may be used to further analyze a locus identified as having an abnormal length according to aspects of the invention.

Accordingly, aspects of the invention relate to detecting abnormal nucleic acid lengths in genomic regions of interest. In some embodiments, the invention aims to estimate the size of genomic regions that are hard to be accessed, such as repetitive elements. However, it should be appreciated that methods of the invention do not require that the precise length be estimated. In some embodiments, it is sufficient to determine that one or more alleles with abnormal lengths are present at a locus of interest (e.g., based on the detection of abnormal capture efficiencies).

In a non-limiting example, fragile X can be used to illustrate aspects of the invention where the size of trinucleotide repeats (genotype) is linked to a symptom (phenotype). However, it should be appreciated that fragile X is a non-limiting example and similar analyses may be performed for other genetic loci (e.g., independently or simultaneously in multiplex analyses).

Use of molecular inversion probes (MIPs) has been demonstrated for detection of single nucleotide polymorphisms (Hardenbol et al. 2005 Genome Res 15:269-75) and for

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preparative amplification of large sets of exons (Porreca et al. 2007 Nat Methods 4:931-6, Krishnakumar et al. 2008 Proc Natl Acad Sci USA 105:9296-301). In both cases, oligonucleotide probes are designed which have ends ('targeting arms') that hybridize up-stream and down-stream of the locus that is to be amplified.

In some embodiments, aspects of the invention are based on the recognition that the effect of length on probe capturing efficiency can be used in the context of an assay (e.g., a high throughput and/or multiplex assay) to allow the length of sequences to be determined without requiring sequencing of the entire region being evaluated. This is particularly useful for repeat regions that are prone to changes in size. As illustrated in FIG. 8, which is reproduced from Deng et al., Nature Biotech. 27:353-60, (see Supplemental Fig. 1G of Deng et al.,) illustrates that shorter sequences are captured with higher efficiency that longer sequences using MIPs. The statistical package R and its *effects* module were used for this analysis. A linear model was used, and each individual factor was assumed to be independent. The dashed lines represent a 95% confidence interval. Shorter target sequences were captured with higher efficiency than long target sequences ($p < 2x10^{-16}$). However, the use of this differential capture efficiency for systematic sequence length analysis was not previously recognized.

In some embodiments, following probe hybridization, polymerase fill-in and ligation reactions are performed to convert the hybridized probe to a covalently-closed, circular molecule containing the desired target. PCR or rolling circle amplification plus exonuclease digestion of non-circularized material is performed to isolate and amplify the circular targets from the starting nucleic acid pool. Since one of the main benefits of the method is the potential for a high degree of multiplexing, generally thousands of targets are captured in a single reaction containing thousands of probes.

According to aspects of the invention, repetitive regions are surrounded by non-repetitive unique sequences, which can be used to amplify the repeat-containing regions using, for example, PCR or padlock (MIP)-based method.

In addition to the repetitive regions, a probe (e.g., a MIP or padlock probe) can be designed to include at least a sequence that is sufficient to be uniquely identified in the genome (or target pool). After the probe is circularized and amplified, the amplicon can be end-sequenced so that the unique sequence can be identified and served as the "representative" of the repetitive region as illustrated in FIG. 9. FIG. 9 illustrates a non-limiting scheme of padlock (MIP) capture of a region that includes both repetitive

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regions (thick wavy line) and the adjacent unique sequence (thick strait line). The regions of the probe are indicated with the targeting arms shown as regions "1" and "3." An intervening region that may be, or include, a sequencing primer binding site is shown as "2." After the padlock is circularized and amplified, it can be end-sequenced to obtain the sequence of the unique sequence, which represents the repetitive region of interest. Although capturing efficiency is overall negatively correlated with target length, different probe sequences may have unique features. Therefore, multiple probes could be designed and tested so that an optimal one is chosen to be sensitive enough to differentiate repetitive sizes of roughly 0-150bp, 150-600bp, and beyond, which represent normal, premutation and full mutation of fragile X syndrome, respectively. However, it should be appreciated that other probe sizes and sequences can be designed, and optionally optimized, to distinguish a range of repeat region size differences (e.g., length differences of about 3-30 bases, about 30-60 bases, about 60-90 bases, about 90-120 bases, about 120-150 bases, about 150-300 bases, about 300-600 bases, about 600-900 bases, or any intermediate or longer length difference). It should be appreciated that a length difference may be an increase in size or a decrease in size.

In some embodiments, an initial determination of an unexpected capture frequency is indicative of the presence of size difference. In some embodiments, an increase in capture frequency is indicative of a deletion. In some embodiments, a decrease in capture frequency is indicative of an insertion. However, it should be appreciated that depending on specific sequence parameters and the relative sizes of the capture probes, the target region, and the deletions or insertions, a change in capture frequency can be associated with either an increase or decrease in target region length. In some embodiments, the precise nature of the change can be determined using one or more additional techniques as described herein.

Accordingly, in some aspects a MIP probe includes a linear nucleic acid strand that contains two hybridization sequences or targeting arms, one at each end of the linear probe, wherein each of the hybridization sequences is complementary to a separate sequence on a the same strand of a target nucleic acid, and wherein these sequences on the target nucleic acid flank the two ends of the target nucleic acid sequence of interest. It should be appreciated that upon hybridization, the two ends of the probe are inverted with respect to each other in the sense that both 5' and 3' ends of the probe hybridize to

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the same strand to separate regions flanking the target region (as illustrated in FIG. 9 for example).

In some embodiments, the hybridization sequences are between about 10-100 nucleotides long, for example between about 10-30, about 30-60, about 60-90, or about 20, about 30, about 40, or about 50 nucleotides long. However, other lengths may be used depending on the application. In some embodiments, the hybridization Tms of both targeting arms of a probe are designed or selected to be similar. In some embodiments, the hybridization Tms of the targeting arms of a plurality of probes designed to capture different target regions are selected or designed to be similar so that they can be used together in a multiplex reaction. Accordingly, a typical size of a MIP probe prior to fill-in is about 60-80 nucleotides long. However, other sizes can be used depending on the sizes of the targeting arms and any other sequences (e.g., primer binding or tag sequences) that are present in the MIP probe. In some embodiments, MIP probes are designed to avoid sequence-dependent secondary structures. In some embodiments, MIP probes are designed such that the targeting arms do not overlap with known polymorphic regions. In some embodiments, targeting arms that can be used for capturing the repeat region of the Fragile X locus can have the following sequences or complementary to these sequences depending on the strand that is captured.

left: CTCCGTTTCGGTTTCACTTC (SEQ ID NO: 181)

right: ATCTTCTCTTCAGCCCTGCT (SEQ ID NO: 182)

The typical captured size using these targeting arms is about 100 nucleotides in length (e.g., about 30 repeats of a tri-nucleotide repeat).

In some embodiments, the number of reads obtained for the "representative" of the repetitive region is not informative to estimate the target length because it is dependent on the total number of reads obtained. To overcome this, it is useful to include one or more probes that target other "control" regions where no or minimal polymorphism exists among populations. Because of the systematic consistency of capturing efficiency (see, e.g., FIG. 9), the ratio of reads obtained for the repetitive "representative" to reads obtained for the control region(s) will be tuned using DNA with defined numbers of repeats. Ultimately, the ratio can serve as a measure of the repeat length as illustrated in FIG. 10. FIG. 10 illustrates a non-limiting hypothetical relationship between target gap size and the relative number of reads of the repetitive

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region, which is measured by the ratio of the repeat "representative" reads vs. the "control" region reads. The unit of y-axis is arbitrary.

In some embodiments, to better tell targets with similar size range apart, the whole repetitive region can be sequenced by making a shotgun library (e.g., by making a shotgun library from a captured sequence, for example a sequence captured using a MIP probe). The longer the repeat is, the more short reads of repeats will be obtained. Therefore, the target length will contribute twice to the relative number of "repetitive" reads, which will gain better resolution of differentiating targets. In some embodiments, the expectation is that the number of reads from any given repeat will be a direct function of the number of repeats present. However, in some embodiments, a Poisson sampling-induced spread may need to be considered and in some embodiments may be sufficiently large to limit the resolution.

When a precise measurement of the length of both alleles from a diploid sample is desired, further manipulations may be required. This is because the capture efficiency measured will actually be the average efficiency of the two alleles. To effectively achieve separate measurements for each allele, barcodes (e.g., sequence tags) can be used that allow the efficiency of individual capture events (from individual genomic loci) to be followed. FIG. 11A-C shows the approach. For a given locus, MIPs are synthesized to contain one of a large number differentiator tags in their backbone such that the probability of any two MIPs in a reaction having the same differentiator tag sequence is low. MIP capture is performed on the sample; the reaction will be biased for shorter target lengths, and therefore the reaction product will be comprised of more 'short' circles than 'long' circles. Each circle should bear a unique differentiator tag sequence. Then, linear RCA (lRCA) is performed on the circles. In the lRCA reaction, circles are converted into long, linear concatemers of themselves. The lRCA reaction for a given circle stops when the concatemer has reached a 'fixed' length (based on the processivity/error rate of the polymerase). Concatemers derived from smaller circles will therefore contain more copies of the differentiator tag, and concatemers derived from larger circles will contain fewer copies of the differentiator tag. The number of each differentiator tag sequence is counted, for example, by next-generation sequencing. When number of occurrences is plotted against differentiator tag ID, the data will naturally cluster into two groups reflecting the lengths of the two alleles in the diploid sample. The allele lengths can therefore be read directly off this graph, after absolute

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length calibration using known standards. In some embodiments, a sequencing technique (e.g., a next-generation sequencing technique) is used to sequence part of one or more captured targets (e.g., or amplicons thereof) and the sequences are used to count the number of different barcodes that are present. Accordingly, in some embodiments, aspects of the invention relate to a highly-multiplexed qPCR reaction.

Other non-limiting examples of loci at which insertions or deletions or repeat sequences may be associated with a disease or condition are provided in Tables 3 and 4. It should be appreciated that the presence of an abnormal length at any one or more of these loci may be evaluated according to aspects of the invention. In some embodiments, two or more of these loci or other loci may be evaluated in a single multiplex reaction using different probes designed to hybridize under the same reaction conditions to different target nucleic acid in a biological sample.

Table 3.

Polyglutamine (PolyQ) Diseases

Type	Gene	Normal/wildtype	Pathogenic
DRPLA (Dentatorubropallidoluysian atrophy)	ATN1 or DRPLA	6 - 35	49 - 88
HD (Huntington's disease)	HTT (Huntingtin)	10 - 35	35+
SBMA (Spinobulbar muscular atrophy or Kennedy disease)	Androgen receptor on the X chromosome.	9 - 36	38 - 62
SCA1 (Spinocerebellar ataxia Type 1)	ATXN1	6 - 35	49 - 88
SCA2 (Spinocerebellar ataxia Type 2)	ATXN2	14 - 32	33 - 77
SCA3 (Spinocerebellar ataxia Type 3 or Machado-Joseph disease)	ATXN3	12 - 40	55 - 86
SCA6 (Spinocerebellar ataxia Type 6)	CACNA1A	4 - 18	21 - 30
SCA7 (Spinocerebellar ataxia Type 7)	ATXN7	7 - 17	38 - 120
SCA17 (Spinocerebellar ataxia Type 17)	TBP	25 - 42	47 - 63

Table 4.

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Non-Polyglutamine Diseases

Type	Gene	Codon	Normal/wildtype	Pathogenic
FRAXA (Fragile X syndrome)	*FMR1*, on the X-chromosome	**CGG**	6 - 53	230+
FXTAS (Fragile X-associated tremor/ ataxia syndrome)	*FMR1*, on the X-chromosome	**CGG**	6 - 53	55-200
FRAXE (Fragile XE mental retardation)	AFF2 or FMR2, on the X-chromosome	**GCC**	6 - 35	200+
FRDA (Friedreich's ataxia)	FXN or X25, (frataxin)	**GAA**	7 - 34	100+
DM (Myotonic dystrophy)	DMPK	**CTG**	5 - 37	50+
SCA8 (Spinocerebellar ataxia Type 8)	OSCA or SCA8	**CTG**	16 - 37	110 – 250
SCA12 (Spinocerebellar ataxia Type 12)	PPP2R2B or SCA12	**CAG** On 5' end	7 - 28	66 - 78

The following examples illustrate aspects and embodiments of the invention and are not intended to be limiting or restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

4. Increasing detection sensitivity:

In some embodiments, aspects of the invention relate to methods for increasing the sensitivity of nucleic acid detection assays.

There are currently many genomic assays that utilize next-generation (e.g., polony-based) sequencing to generate data, including genome resequencing, RNA-seq for gene expression, bisulphite sequencing for methylation, and Immune-seq, among others. In order to make quantitative measurements (including genotype calling), these

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methods utilize the counts of sequencing reads of a given genomic locus as a proxy for the representation of that sequence in the original sample of nucleic acids. The majority of these techniques require a preparative step to construct a high-complexity library of DNA molecules that is representative of a sample of interest. Current assays use one of several alternative nucleic acid preparative techniques (e.g., amplification, for example PCR-based amplification; sequence-specific capture, for example, using immobilized capture probes; or target capture into a circularized probe followed by a sequence analysis step. In order to reduce errors associated with the unpredictability (stochastic nature) of nucleic acid isolation and sequence analysis techniques, current methods involve oversampling a target nucleic acid preparation in order to increase the likelihood that all sequences that are present in the original nucleic acid sample will be represented in the final sequence data. For example, a genomic sequencing library may contain an over- or under-representation of particular sequences from a source nucleic acid sample (e.g., genome preparation) as a result of stochastic variations in the library construction process. Such variations can be particularly problematic when they result in target sequences from a genome being absent or undetectable in a sequencing library. For example, an under-representation of particular allelic sequences (e.g., heterozygotic alleles) from a genome in a sequencing library can result in an apparent homozygous representation in a sequencing library.

In contrast, aspects of the invention relate to basing a nucleic acid sequence analysis on results from two or more different nucleic acid preparatory techniques that have different systematic biases in the types of nucleic acids that they sample rather than simply oversampling the target nucleic acid. According to some embodiments, different techniques have different sequence biases that are systematic and not simply due to stochastic effects during nucleic acid capture or amplification. Accordingly, in some embodiments, the degree of oversampling required to overcome variations in nucleic acid preparation needs to be sufficient to overcome the biases. In some embodiments, the invention provides methods that reduce the need for oversampling by combining nucleic acid and/or sequence results obtained from two or more different nucleic acid preparative techniques that have different biases.

According to the invention, different techniques have different characteristic or systematic biases. For example, one technique may bias a sample analysis towards one

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particular allele at a genetic locus of interest, whereas a different technique would bias the sample analysis towards a different allele at the same locus. Accordingly, the same sample may be identified as being different depending on the type of technique that is used to prepare nucleic acid for sequence analysis. This effectively represents a sensitivity issue, because each technique has a different relative sensitivities for polymorphic sequences of interest.

According to aspects of the invention, the sensitivity of a nucleic acid analysis can be increased by combining the sequences from different nucleic acid preparative steps and using the combined sequence information for a diagnostic assay (e.g., for a making a call as to whether a subject is homozygous or heterozygous at a genetic locus of interest).

Currently, the ability of DNA sequencing to detect mutations is limited by the ability of the upstream sample isolation (e.g., by amplification, immobilization enrichment, circularization capture, etc.) methods to reliably isolate the locus of interest. If one wishes to make heterozygote base-calls for a diploid genome (e.g. a human sample presented for molecular diagnostic sequencing), it is important in some embodiments that the isolation method produces near- or perfectly- uniform amounts of the two alleles to be sequenced (at least sufficiently uniform to be "called" unambiguously as a heterozygote or a homozygote for a locus of interest).

Sample preparative methods may fall into three classes: 1) single- or several-target amplification (e.g., uniplex PCR, 'multiplex' PCR), 2) multi-target hybridization enrichment (e.g., Agilent SureSelect 'hybrid capture' [Gnirke et al 2009, *Nature methods* 27:182-9], Roche/Nimblegen 'sequence capture' [Hodges et al 2007, *Nature genetics* 39:1522-7], and 3) multi-target circularization selection (e.g. molecular inversion probes or padlock probes, [Porreca et al 2007, *Nature methods* 4:931-6, Turner et al 2009, *Nature methods* 6:315-6], 'selectors' [Dahl et al 2005, *Nucleic acids research* 33:e71]). Each of these methods can result in a pool of isolated product that does not adequately represent the input abundance distribution. For example, the two alleles at a heterozygous position can become skewed far from their input 50:50 ratio to something that results in a missed basecall during downstream sequencing. For example, if the ratio was skewed from 50:50 to 10:90, and the sample was sequenced to 10X average coverage, there is a high probability that one of the two alleles would not be observed once in the ten sequencing reads. This would reduce the sensitivity of the sequencing

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method by converting a heterozygous position to homozygous (where potentially the 'mutant' allele was the one not observed). In some embodiments, a skewed ratio is a particular issue that decreases the sensitivity of detecting mutations present in a heterogeneous tumor tissue. For example, if only 10% of the cells analyzed in a heterogeneous sample harbored a heterozygous mutation, the mutation would be expected to be present in 5% of sequence reads, not 50%. In this scenario, the need for robust, sensitive detection may be even more acute.

The methods disclosed herein are based, in part, on the discovery that certain classes of isolation methods have different modes of bias. The disclosure provide methods for increasing the sensitivity of the downstream sequencing by using a combination of multiple isolation methods (e.g., one or more from at least two of the classes disclosed herein) for a sample. This is particularly important in molecular diagnostics where high sensitivity is required to minimize the chances of 'missing' a disease-associated mutation. For example, given a nominal false-negative error rate of $1x10^{-3}$ for sequencing following circularization selection, and a false-negative error rate of $1x10^{-3}$ for sequencing following hybridization enrichment, one can achieve a final false-negative rate of $1x10^{-6}$ by performing both techniques on the sample (assuming failures in each method are fully independent). For a recessive disease with carrier frequency of 0.1, caused by a single fully-penetrant mutant allele, the number of missed carrier diagnoses would decrease from 1000 per million patients tested to 1 per million patients tested. Furthermore, if the testing was used in the context of prenatal carrier screening, the number of affected children born as a result of missing the carrier call in one parent would decrease from 25 per million to 25 per billion born.

Additionally, the disclosure provides combinations of preparative methods to effectively increase sequencing coverage in regions containing disease-associated alleles. Since heterozygote error rate is largely tied to both deviations from 50:50 allele representation, and in the case of next-generation DNA sequencing deviations from average abundance (such that less abundant isolated targets are more likely to be undersampled at one or both alleles), selectively increasing coverage in these regions will also selectively increase sensitivity. Furthermore, MIPs that detect presence or absence of specific known disease-associated mutations can be used to increase sensitivity selectively. In some embodiments, these MIPs would have a targeting arm whose 3' –most region is complementary to the expected mutation, and has a fill-in

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length of 0 or more bp. Thus, the MIP will form only if the mutation is present, and its presence will be detected by sequencing.

Additionally, algorithms disclosed herein may be used to determine base identity with varying levels of stringency depending on whether the given position has any known disease-associated alleles. Stringency can be reduced in such positions by decreasing the minimum number of observed mutant reads necessary to make a consensus base-call. This will effectively increase sensitivity for mutant allele detection at the cost of decreased specificity.

An embodiment of the invention combines MIPs plus hybridization enrichment, plus optionally extra MIPs targeted to specific known, common disease-associated loci, e.g., to detect the presence of a polymorphism in a target nucleic acid. A non-limiting example is illustrated in FIG. 12 that illustrates a schematic using MIPs plus hybridization enrichment, plus optionally extra MIPs targeted to specific known, common disease-associated loci, e.g., to detect the presence of a polymorphism in a target nucleic acid.

FIGs. 13 and 14 illustrate different capture efficiencies for MIP-based captures. FIG. 13 shows a graph of per-target abundance with MIP capture. In this graph, bias largely drives the heterozygote error rate, since targets which are less abundant here are less likely to be covered in sufficient depth during sequencing to adequately sample both alleles. This is from Turner et al 2009, Nature methods 6:315-6. Hybridization enrichment results in a qualitatively similar abundance distribution, but the abundance of a given target is likely not correlated between the two methods. FIG. 14 shows a graph of correlation between two MIP capture reactions from Ball et al 2009, Nature biotechnology 27:361-8. Each point represents the target abundance in replicate 1 and replicate 2. Pearson correlation r=0.956. This indicates that MIP capture reproducibly biases targets to specific abundances. Hybridization enrichment is similarly correlated from one capture to the next.

According to aspects of the invention, such biases can be detected or overcome by systematically combining different capture and/or analytical techniques in an assay that interrogates a plurality of loci in a plurality of subject samples.

Accordingly, it should be appreciated that in any of the embodiments described herein (e.g., tiling/staggering, tagging, size-detection, sensitivity enhancing algorithms,

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or any combination thereof), aspects of the invention involve preparing genomic nucleic acid and/or contacting them with one or more different probes (e.g., capture probes, hybridization probes, MIPs, others etc.). In some embodiments, the amount of genomic nucleic acid used per subject ranges from 1 ng to 10 micrograms (e.g., 500 ng to 5 micrograms). However, higher or lower amounts (e.g., less than 1 ng, more than 10 micrograms, 10-50 micrograms, 50-100 micrograms or more) may be used. In some embodiments, for each locus of interest, the amount of probe used per assay may be optimized for a particular application. In some embodiments, the ratio (molar ratio, for example measured as a concentration ratio) of probe to genome equivalent (e.g., haploid or diploid genome equivalent, for example for each allele or for both alleles of a nucleic acid target or locus of interest) ranges from 1/100, 1/10, 1/1, 10/1, 100/1, 1000/1. However, lower, higher, or intermediate ratios may be used.

In some embodiments, the amount of target nucleic acid and probe used for each reaction is normalized to avoid any observed differences being caused by differences in concentrations or ratios. In some embodiments, in order to normalize genomic DNA and probe, the genomic DNA concentration is read using a standard spectrophotometer or by fluorescence (e.g., using a fluorescent intercalating dye). The probe concentration may be determined experimentally or using information specified by the probe manufacturer.

Similarly, once a locus has been captured (e.g., on a MIP or other probe or in another form), it may be amplified and/or sequenced in a reaction involving one or more primers. The amount of primer added for each reaction can range from 0.1 pmol to 1 nmol, 0.15 pmol to 1.5 nmol (for example around 1.5 pmol). However, other amounts (e.g., lower, higher, or intermediate amounts) may be used.

In some embodiments, it should be appreciated that one or more intervening sequences (e.g., sequence between the first and second targeting arms on a MIP capture probe), identifier or tag sequences, or other probe sequences that are not designed to hybridize to a target sequence (e.g., a genomic target sequence) should be designed to avoid excessive complementarity (to avoid cross-hybridization) to target sequences or other sequences (e.g., other genomic sequences) that may be in a biological sample. For example, these sequences may be designed have a sufficient number of mismatches with any genomic sequence (e.g., at least 5, 10, 15, or more mismatches out of 30 bases) or as having a Tm (e.g., a mismatch Tm) that is lower (e.g., at least 5, 10, 15, 20, or more degrees C lower) than the hybridization reaction temperature.

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It should be appreciated that a targeting arm as used herein may be designed to hybridize (e.g., be complementary) to either strand of a genetic locus of interest if the nucleic acid being analyzed is DNA (e.g., genomic DNA). However, in the context of MIP probes, whichever strand is selected for one targeting arm will be used for the other one. However, in the context of RNA analysis, it should be appreciated that a targeting arm should be designed to hybridize to the transcribed RNA. It also should be appreciated that MIP probes referred to herein as "capturing" a target sequence are actually capturing it by template-based synthesis rather than by capturing the actual target molecule (other than for example in the initial stage when the arms hybridize to it or in the sense that the target molecule can remain bound to the extended MIP product until it is denatured or otherwise removed).

It should be appreciated that in some embodiments a targeting arm may include a sequence that is complementary to one allele or mutation (e.g., a SNP or other polymorphism, a mutation, etc.) so that the probe will preferentially hybridize (and capture) target nucleic acids having that allele or mutation. However, in many embodiments, each targeting arm is designed to hybridize (e.g., be complementary) to a sequence that is not polymorphic in the subjects of a population that is being evaluated. This allows target sequences to be captured and/or sequenced for all alleles and then the differences between subjects (e.g., calls of heterozygous or homozygous for one or more loci) can be based on the sequence information and/or the frequency as described herein.

It should be appreciated that sequence tags (also referred to as barcodes) may be designed to be unique in that they do not appear at other positions within a probe or a family of probes and they also do not appear within the sequences being targeted. Thus they can be used to uniquely identify (e.g., by sequencing or hybridization properties) particular probes having other characteristics (e.g., for particular subjects and/or for particular loci).

It also should be appreciated that in some embodiments probes or regions of probes or other nucleic acids are described herein as comprising or including certain sequences or sequence characteristics (e.g., length, other properties, etc.). However, it should be appreciated that in some embodiments, any of the probes or regions of probes or other nucleic acids consist of those regions (e.g., arms, central regions, tags, primer sites, etc., or any combination thereof) of consist of those sequences or have sequences with characteristics that consist of one or more characteristics (e.g., length, or other

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properties, etc.) as described herein in the context of any of the embodiments (e.g., for tiled or staggered probes, tagged probes, length detection, sensitivity enhancing algorithms or any combination thereof).

It should be appreciated that probes, primers, and other nucleic acids designed or used herein may be synthetic, natural, or a combination thereof. Accordingly, as used herein, the term "nucleic acid" refers to multiple linked nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to an exchangeable organic base, which is either a pyrimidine (e.g., cytosine (C), thymidine (T) or uracil (U)) or a purine (e.g., adenine (A) or guanine (G)). "Nucleic acid" and "nucleic acid molecule" may be used interchangeably and refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms shall also include polynucleosides (i.e., a polynucleotide minus a phosphate) and any other organic base containing nucleic acid. The organic bases include adenine, uracil, guanine, thymine, cytosine and inosine. Unless otherwise stated, nucleic acids may be single or double stranded. The nucleic acid may be naturally or non-naturally occurring. Nucleic acids can be obtained from natural sources, or can be synthesized using a nucleic acid synthesizer (i.e., synthetic). Harvest and isolation of nucleic acids are routinely performed in the art and suitable methods can be found in standard molecular biology textbooks. (See, for example, Maniatis' Handbook of Molecular Biology.) The nucleic acid may be DNA or RNA, such as genomic DNA, mitochondrial DNA, mRNA, cDNA, rRNA, miRNA, or a combination thereof. Non-naturally occurring nucleic acids such as bacterial artificial chromosomes (BACs) and yeast artificial chromosomes (YACs) can also be used.

The invention also contemplates the use of nucleic acid derivatives. As will be described herein, the use of certain nucleic acid derivatives may increase the stability of the nucleic acids of the invention by preventing their digestion, particularly when they are exposed to biological samples that may contain nucleases. As used herein, a nucleic acid derivative is a non-naturally occurring nucleic acid or a unit thereof. Nucleic acid derivatives may contain non-naturally occurring elements such as non-naturally occurring nucleotides and non-naturally occurring backbone linkages.

Nucleic acid derivatives may contain backbone modifications such as but not limited to phosphorothioate linkages, phosphodiester modified nucleic acids, phosphorothiolate modifications, combinations of phosphodiester and phosphorothioate nucleic acid, methylphosphonate, alkylphosphonates, phosphate esters,

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alkylphosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, carboxymethyl esters, methylphosphorothioate, phosphorodithioate, p-ethoxy, and combinations thereof. The backbone composition of the nucleic acids may be homogeneous or heterogeneous.

Nucleic acid derivatives may contain substitutions or modifications in the sugars and/or bases. For example, they include nucleic acids having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 3' position and other than a phosphate group at the 5' position (e.g., an 2'-O-alkylated ribose group). Nucleic acid derivatives may include non-ribose sugars such as arabinose. Nucleic acid derivatives may contain substituted purines and pyrimidines such as C-5 propyne modified bases, 5-methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, 2-thiouracil and pseudoisocytosine. In some embodiments, substitution(s) may include one or more substitutions/modifications in the sugars/bases, groups attached to the base, including biotin, fluorescent groups (fluorescein, cyanine, rhodamine, etc), chemically-reactive groups including carboxyl, NHS, thiol, etc., or any combination thereof.

A nucleic acid may be a peptide nucleic acid (PNA), locked nucleic acid (LNA), DNA, RNA, or co-nucleic acids of the same such as DNA-LNA co-nucleic acids. PNA are DNA analogs having their phosphate backbone replaced with 2-aminoethyl glycine residues linked to nucleotide bases through glycine amino nitrogen and methylenecarbonyl linkers. PNA can bind to both DNA and RNA targets by Watson-Crick base pairing, and in so doing form stronger hybrids than would be possible with DNA or RNA based oligonucleotides in some cases.

PNA are synthesized from monomers connected by a peptide bond (Nielsen, P.E. et al. Peptide Nucleic Acids, Protocols and Applications, Norfolk: Horizon Scientific Press, p. 1-19 (1999)). They can be built with standard solid phase peptide synthesis technology. PNA chemistry and synthesis allows for inclusion of amino acids and polypeptide sequences in the PNA design. For example, lysine residues can be used to introduce positive charges in the PNA backbone. All chemical approaches available for the modifications of amino acid side chains are directly applicable to PNA. Several types of PNA designs exist, and these include single strand PNA (ssPNA), bisPNA and pseudocomplementary PNA (pcPNA).

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The structure of PNA/DNA complex depends on the particular PNA and its sequence. ssPNA binds to single stranded DNA (ssDNA) preferably in antiparallel orientation (i.e., with the N-terminus of the ssPNA aligned with the 3' terminus of the ssDNA) and with a Watson-Crick pairing. PNA also can bind to DNA with a Hoogsteen base pairing, and thereby forms triplexes with double stranded DNA (dsDNA) (Wittung, P. et al., *Biochemistry* 36:7973 (1997)).

A locked nucleic acid (LNA) is a modified RNA nucleotide. An LNA form hybrids with DNA, which are at least as stable as PNA/DNA hybrids (Braasch, D.A. et al., *Chem & Biol.* 8(1):1-7(2001)). Therefore, LNA can be used just as PNA molecules would be. LNA binding efficiency can be increased in some embodiments by adding positive charges to it. LNAs have been reported to have increased binding affinity inherently.

Commercial nucleic acid synthesizers and standard phosphoramidite chemistry are used to make LNAs. Therefore, production of mixed LNA/DNA sequences is as simple as that of mixed PNA/peptide sequences. The stabilization effect of LNA monomers is not an additive effect. The monomer influences conformation of sugar rings of neighboring deoxynucleotides shifting them to more stable configurations (Nielsen, P.E. et al. Peptide Nucleic Acids, Protocols and Applications, Norfolk: Horizon Scientific Press, p. 1-19 (1999)). Also, lesser number of LNA residues in the sequence dramatically improves accuracy of the synthesis. Most of biochemical approaches for nucleic acid conjugations are applicable to LNA/DNA constructs.

These and other aspects of the invention are illustrated by the following non-limiting examples.

EXAMPLES

The following examples illustrate non-limiting embodiments of the invention.

Example 1: Design a set of capture probes for a human target exon

All targets are captured as a set of partially-overlapping subtargets. For example, in the tiling approach, a 200 bp target exon might be captured as a set of 12 subtargets,

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each 60bp in length (FIG. 1). Each subtarget is chosen such that it partially overlaps two or three other targets.

In some embodiments, all probes are composed of three regions: 1) a 20 bp 'targeting arm' comprised of sequence which hybridizes immediately upstream from the sub-target, 2) a 30 bp 'constant region' comprised of sequence used as a pair of amplification priming sites, and 3) a second 20 bp 'targeting arm' comprised of sequence which hybridizes immediately downstream from the sub-target. Targeting arm sequences will be different for each capture probe in a set, while constant region sequence will be the same for all probes in the set, allowing all captured targets to be amplified with a single set of primers. Targeting arm sequences should be designed such that any given pair of 20 bp sequences is unique in the target genome (to prevent spurious capture of undesired sites). Additionally, melting temperatures should be matched for all probes in the set such that hybridization efficiency is uniform for all probes at a constant temperature (e.g., 60 C). Targeting arm sequences should be computationally screened to ensure they do not form strong secondary structure that would impair their ability to basepair with the genomic target.

Hybridize capture probes to human genomic sample

Assemble hybridization reaction:

- 1.0 ul capture probe mix (~2.5 pmol)
- 2.0 ul 10X Ampligase buffer (Epicentre)
- 6.0 ul 500 ng/ul human genomic DNA (~16.7 fmol)
- 11 ul dH2O

In a thermal cycler, heat reaction to 95C for 5 min to denature genomic DNA, then cool to 60C. Allow to incubate at 60C for 40 hours.

Convert hybridized probes into covalently-closed circular products containing subtargets

Prepare fill-in / ligation reaction mixture:

- 0.25 ul 2 mM dNTP mix (Invitrogen)
- 2.5 ul 10X Ampligase buffer (Epicentre)
- 5.0 ul 5 U/ul Taq Stoffel fragment (Applied Biosystems)

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- 12.5 ul 5 U/ul Ampligase (Epicentre)
- 4.75 ul dH2O

Add 1.0 ul of this mix to the hybridized probe reaction, and incubate at 60C for 10 hours.

Purify circularized probe / subtarget products from un-reacted probes and genomic DNA

Prepare exonuclease reaction mixture:

- 21 ul fill-in / ligation reaction product
- 2.0 ul 10X exonuclease I buffer (New England Biolabs)
- 2.0 ul 20 U/ul exonuclease I (New England Biolabs)
- 2.0 ul 100 U/ul exonuclease III (New England Biolabs)

Incubte at 37C for 60 min, then heat-inactivate by incubating at 80C for 15 min. Immediately cool to 4C for storage.

Amplify circular material by PCR using primers specific to the 'constant region' of the probes

Prepare PCR mixture:

- 5.0 ul 10X Accuprime reaction buffer (Invitrogen)
- 1.5 ul 10 uM CP-2-FA (5'-GCACGATCCGACGGTAGTGT-3') (SEQ ID NO: 183)
- 1.5 ul 10 uM CP-2-RA (5'-CCGTAATCGGGAAGCTGAAG-3') (SEQ ID NO: 184)
-
- 0.4 ul 25 mM dNTP mix (Invitrogen)
- 2.0 ul heat-inactivated exonuclease reaction mix
- 1.5 ul 10X SybrGreen (Invitrogen)
- 0.4 ul 2.5 U/ul Accuprime Pfx polymerase (Invitrogen)
- 37.7 ul dH2O

Thermal cycle in real-time thermal cycler according to the following protocol, but stop cycling before amplification yield plateaus (generally 8-12 cycles):

1. 95C for 5 min

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2. 95C for 30 sec
3. 58C for 60 sec
4. 72C for 60 sec
5. goto 2, N more times

Prepare a shotgun next-generation sequencing library for analysis

- Purify desired amplicon population from non-specific amplification products by gel extraction.
- Concatemerize amplicons into high-molecular weight products suitable for shearing
- Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument. DNA should be sheared into fragments several hundred basepairs in length.
- Ligate adapters required for amplification by the sequencing platform used. If necessary, purify ligated product from unligated product and adapters.

Example 2: Use of differentiator tag sequences to detect and correct bias in a MIP-capture reaction of a set of exon targets

The first step in performing the detection/correction is to determine how many differentiator tag sequences are necessary for the given sample. In this example, 1000 genomic targets corresponding to 1000 exons were captured. Since the differentiator tag sequence is part of the probe, it will measure/report biases that occur from the earliest protocol steps. Also, being located in the backbone, the differentiator tag sequence can easily be sequenced from a separate priming site, and therefore not impact the total achievable read-length for the target sequence. MIP probes are synthesized using standard column-based oligonucleotide synthesis by any number of vendors (e.g. IDT), and differentiator tag sequences are introduced as 'degenerate' positions in the backbone. Each degenerate position increases the total number of differentiator tag sequences synthesized by a factor of 4, so a 10 nt degenerate region implies a differentiator tag sequence complexity of ~1e6 species.

Hybridize capture probes to human genomic sample

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Assemble hybridization reaction:

- 1.0 ul capture probe mix (~2.5 pmol)
- 2.0 ul 10X Ampligase buffer (Epicentre)
- 6.0 ul 500 ng/ul human genomic DNA (~16.7 fmol)
- 11 ul dH2O

In a thermal cycler, heat reaction to 95C for 5 min to denature genomic DNA, then cool to 60C. Allow to incubate at 60C for 40 hours.

Convert hybridized probes into covalently-closed circular products containing subtargets

Prepare fill-in / ligation reaction mixture:

- 0.25 ul 2 mM dNTP mix (Invitrogen)
- 2.5 ul 10X Ampligase buffer (Epicentre)
- 5.0 ul 5 U/ul Taq Stoffel fragment (Applied Biosystems)
- 12.5 ul 5 U/ul Ampligase (Epicentre)
- 4.75 ul dH2O

Add 1.0 ul of this mix to the hybridized probe reaction, and incubate at 60C for 10 hours.

Purify circularized probe / subtarget products from un-reacted probes and genomic DNA

Prepare exonuclease reaction mixture:

- 21 ul fill-in / ligation reaction product
- 2.0 ul 10X exonuclease I buffer (New England Biolabs)
- 2.0 ul 20 U/ul exonuclease I (New England Biolabs)
- 2.0 ul 100 U/ul exonuclease III (New England Biolabs)

Incubate at 37C for 60 min, then heat-inactivate by incubating at 80C for 15 min. Immediately cool to 4C for storage.

Amplify circular material by PCR using primers specific to the 'constant region' of the probes

Prepare PCR mixture:

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- 5.0 ul 10X Accuprime reaction buffer (Invitrogen)
- 1.5 ul 10 uM CP-2-FA (5'-GCACGATCCGACGGTAGTGT-3') (SEQ ID NO: 183)
- 1.5 ul 10 uM CP-2-RA (5'-CCGTAATCGGGAAGCTGAAG-3') (SEQ ID NO: 184)
- 0.4 ul 25 mM dNTP mix (Invitrogen)
- 2.0 ul heat-inactivated exonuclease reaction mix
- 1.5 ul 10X SybrGreen (Invitrogen)
- 0.4 ul 2.5 U/ul Accuprime Pfx polymerase (Invitrogen)
- 37.7 ul dH2O

Thermal cycle in real-time thermal cycler according to the following protocol, but stop cycling before amplification yield plateaus (generally 8-12 cycles):

6. 95C for 5 min
7. 95C for 30 sec
8. 58C for 60 sec
9. 72C for 60 sec
10. goto 2, N more times

Prepare a shotgun next-generation sequencing library for analysis

- Purify desired amplicon population from non-specific amplification products by gel extraction.
- Concatemerize amplicons into high-molecular weight products suitable for shearing
- Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument. DNA should be sheared into fragments several hundred basepairs in lenth.
- Ligate adapters required for amplification by the sequencing platform used. If necessary, purify ligated product from unligated product and adapters.

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Perform sequencing of library according to manufacturer's directions (e.g. Illumina,ABI, etc), reading both the target sequence and the differentiator tag sequence.

Analyze data by correcting for any biases detected by quantitation of differentiator tag sequence abundance

Construct a table of target:differentiator tag abundances from the read data, e.g.:

Target ID	Differentiator tag sequence ID	Count
1	3547	1
2	4762	1
1	9637	1
1	1078	5
3	4762	1
1	2984	1

All 'count' entries should be '1', since any particular target:differentiator tag mapping will not occur more than once by chance, and therefore will only be observed if bias was present somewhere in the sample preparation process. For any target:differentiator tag combination observed more than once, all such reads are 'collapsed' into a single read before consensus basecalls are determined. This will cancel the effect of bias on consensus basecall accuracy. FIG. 5 depicts a method for making diploid genotype calls in which repeat target:differentiator tag combination are collapsed.

Example 3: Differentiator tag sequence design for MIP capture reactions

For a set of targets, the number of differentiator tag sequences necessary to be confident (within some statistical bounds) that a certain differentiator tag sequence will not be observed more than once by chance in combination with a certain target sequence was determined. The total number of unique differentiator tag sequences for a certain differentiator tag sequence length is determined as $4^{(\text{Length in nucleotides of the differentiator tag sequence})}$. For a molecular inversion probe capture reaction that uses MIP probes having differentiator tag sequences, the probability of performing the capture reaction and capturing one or more copies of a target sequence having the same differentiator tag sequence is calculated as: p = 1 - [N! / (N-M)!] / [N^M], wherein N is the total number

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of possible unique differentiator tag sequences and M is the number of target sequence copies in the capture reaction. Thus, by varying the differentiator tag sequence length it is possible to perform a MIP capture reaction in which the probability of capturing one or more copies of a target sequence having the same differentiator tag sequence is set at a predetermined probability value.

For example, for a differentiator tag sequence of 15 nucleotides in length, there are 1,073,741,824 possible differentiator tag sequences. A MIP capture reaction in which MIP probes, each having a differentiator tag sequence of 15 nucleotides, are combined with 10000 target sequence copies (e.g., genome equivalents), the probability of capturing one or more copies of a target sequence having the same differentiator tag sequence is 0.05. In this example, the MIP reaction will produce very few (usually 0, but occasionally 1 or more) targets where multiple copies are tagged with the same differentiator tag sequence. FIG. 6 depicts results of a simulation for 100000 capture reactions having 15 nucleotide differentiator tag sequences and 10000 target sequences.

Example 4: Assessment of the probability for obtaining enough sequencing reads to make accurate base-calls at multiple independent loci, as a function of sequencing coverage.

Monte Carlo simulations were performed to determine sequencing coverage requirements. The simulations assume 10000 genomic copies of a given locus (target) half mom alleles and half dad alleles. The simulations further assume 1% efficiency of capture for the MIP reaction. The simulation samples from a capture mix 100 times without replacement to create a set of 100 capture products. The simulation then samples from the set of 100 capture products with replacement (assuming unbiased amplification) to generate 'reads' from either mom or dad. The number of reads sampled depends on the coverage. The number of independent reads from both mom and dad necessary to make a high-quality base-call (assumed to be 10 or 20 reads) were then determined. The process was repeated 1000 times for each coverage level, and the fraction of times that enough reads from both parents were successfully obtained was determined. This fraction was raised to the power 1000, assuming we have 1000 independent loci that must obtain successful base-calls, plotted (See FIG. 7). Result show that roughly 50x coverage is required to capture each allele >= 10x with > 0.95 probability.

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Example 5: MIP capture of 'target' locus and 'control' loci

In some embodiments, to accurately quantify the efficiency of target locus capture, at least three sets of control loci are captured in parallel that have *a priori* been shown to serve as proxies for various lengths of target locus. For example, if the target locus is expected to have a length between 50 and 1000 bp, then sets of control loci having lengths of 50, 250, and 1000 bp could be captured (e.g. 20 loci per set should provide adequate protection from outliers), and their abundance digitally measured by sequencing. These loci should be chosen such that minimal variation in efficiency between samples and on multiple runs of the same sample is observed (and are therefore 'efficiency invariant'). These will serve as 'reference' points that define the shape of the curve of abundance-vs-length. Determining the length of the target is then simply a matter of 'reading' the length from the appropriate point on the calibration curve.

In some embodiments, the statistical confidence one has in the estimate of target length from this method is driven largely by three factors: 1) reproducibility / variation of the abundance data used to generate the calibration curve; 2) goodness of fit of the regression to the 'control' datapoints; 3) reproducibility of abundance data for the target locus being measured. Statistical bounds on 1) and 2) will be known in advance, having been measured during development of the assay. Additionally, statistical bounds on 3) will be known in general in advance, since assay development should include adequate population sampling and measure of technical reproducibility. Standard statistical methods should be used to combine these three measures into a single *P* value for any given experimental measure of target abundance.

In some embodiments, given the set of calibration observations, and a linear regression fit to that data, the regression can be used to predict the length value for n observations of the target locus whose length is unknown. First, choose an acceptable range for the confidence interval of the length estimate. For example, in the case of distinguishing "normal" (87-93bp) from "premutation" (165-600bp) potential cases of Fragile X, the goal is to measure length to sufficient precision to distinguish 93 bp from 165 bp. The predicted response value, computed when n observations is substituted into the equation for the regressed line, will have arbitrary precision. However, if for example a 95% confidence level is desired, that 95% confidence interval must be sufficiently short that it does not overlap both the "normal" and "premutation" length

ranges. Continuing the example, if one calculates a length of 190 from n=400 MIP observations, and based on the regression from calibration data, the 95% confidence interval is 190 +/- 20 bp, one can conclude the sample represents a "premutation" length with 95% certainty. Conversely, if the calibration data were less robust, error estimates of the regression would be higher, leading to larger confidence intervals on the predicted response value. In some embodiments, if the 95% CI were calculated as 190 +/- 100 bp from n=400, one could not determine whether the predicted response value corresponds to a "normal" or "premutation" length.

In some embodiments, the confidence interval for a predicted response is calculated as:

The estimate for the response $\hat{y}$ *is identical to the estimate for the mean of the response:* $\hat{y} = b_0 + b_1 x^*$. *The confidence interval for the predicted value is given by* $\hat{y} \pm t^* s_{\hat{y}}$, *where* $\hat{y}$ *is the fitted value corresponding to* x^*. *The value* t^* *is the upper (1 - C)/2 critical value for the t(n - 2) distribution.*

In some embodiments, a technique for analyzing a locus of interest can involve the following steps.

Convert hybridized probes into covalently-closed circular products containing subtargets

Prepare fill-in / ligation reaction mixture:

- 0.25 ul 2 mM dNTP mix (Invitrogen)
- 2.5 ul 10X Ampligase buffer (Epicentre)
- 5.0 ul 5 U/ul Taq Stoffel fragment (Applied Biosystems)
- 12.5 ul 5 U/ul Ampligase (Epicentre)
- 4.75 ul dH2O

Add 1.0 ul of this mix to the hybridized probe reaction, and incubate at 60C for 10 hours.

Purify circularized probe / subtarget products from un-reacted probes and genomic DNA

Prepare exonuclease reaction mixture:

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- 21 ul fill-in / ligation reaction product
- 2.0 ul 10X exonuclease I buffer (New England Biolabs)
- 2.0 ul 20 U/ul exonuclease I (New England Biolabs)
- 2.0 ul 100 U/ul exonuclease III (New England Biolabs)

Incubte at 37C for 60 min, then heat-inactivate by incubating at 80C for 15 min. Immediately cool to 4C for storage.

Amplify circular material by PCR using primers specific to the 'constant region' of the probes

Prepare PCR mixture:

- 5.0 ul 10X Accuprime reaction buffer (Invitrogen)
- 1.5 ul 10 uM CP-2-FA-Ilmn (platform-specific amplification sequence plus 'circle constant region'-specific sequence)
- 1.5 ul 10 uM CP-2-RA-Ilmn (platform-specific amplification sequence plus 'circle constant region'-specific sequence)
- 0.4 ul 25 mM dNTP mix (Invitrogen)
- 2.0 ul heat-inactivated exonuclease reaction mix
- 1.5 ul 10X SybrGreen (Invitrogen)
- 0.4 ul 2.5 U/ul Accuprime Pfx polymerase (Invitrogen)
- 37.7 uldH2O

Thermal cycle in real-time thermal cycler according to the following protocol, but stop cycling before amplification yield plateaus (generally 8-12 cycles):

11. 95C for 5 min
12. 95C for 30 sec
13. 58C for 60 sec
14. 72C for 60 sec
15. goto 2, N more times

Perform sequencing (e.g., next-generation sequencing) on sample for digital quantitation according to manufacturer's instructions (e.g., Illumina, ABI)

Example 6: MIP-capture reaction of a set of exon target nucleic acids

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MIP probes are synthesized using standard column-based oligonucleotide synthesis by any number of vendors (e.g. IDT).

Hybridize capture probes to human genomic sample

Assemble hybridization reaction:

- 1.0 ul capture probe mix (~2.5 pmol)
- 2.0 ul 10X Ampligase buffer (Epicentre)
- 6.0 ul 500 ng/ul human genomic DNA (~16.7 fmol)
- 11 ul dH2O

In a thermal cycler, heat reaction to 95C for 5 min to denature genomic DNA, then cool to 60C. Allow to incubate at 60C for 40 hours.

Convert hybridized probes into covalently-closed circular products containing target nucleic acids

Prepare fill-in / ligation reaction mixture:

- 0.25 ul 2 mM dNTP mix (Invitrogen)
- 2.5 ul 10X Ampligase buffer (Epicentre)
- 5.0 ul 5 U/ul Taq Stoffel fragment (Applied Biosystems)
- 12.5 ul 5 U/ul Ampligase (Epicentre)
- 4.75 ul dH2O

Add 1.0 ul of this mix to the hybridized probe reaction, and incubate at 60C for 10 hours.

Purify circularized probe/target nucleic acid products from un-reacted probes and genomic DNA

Prepare exonuclease reaction mixture:

- 21 ul fill-in / ligation reaction product
- 2.0 ul 10X exonuclease I buffer (New England Biolabs)
- 2.0 ul 20 U/ul exonuclease I (New England Biolabs)
- 2.0 ul 100 U/ul exonuclease III (New England Biolabs)

Incubate at 37C for 60 min, then heat-inactivate by incubating at 80C for 15 min. Immediately cool to 4C for storage.

Amplify circular material by PCR using primers specific to the 'constant region' of the probes

Prepare PCR mixture:

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- 5.0 ul 10X Accuprime reaction buffer (Invitrogen)
- 1.5 ul 10 uM CP-2-FA (5'-GCACGATCCGACGGTAGTGT-3') (SEQ ID NO: 183)
- 1.5 ul 10 uM CP-2-RA (5'-CCGTAATCGGGAAGCTGAAG-3') (SEQ ID NO: 184)
- 0.4 ul 25 mM dNTP mix (Invitrogen)
- 2.0 ul heat-inactivated exonuclease reaction mix
- 1.5 ul 10X SybrGreen (Invitrogen)
- 0.4 ul 2.5 U/ul Accuprime Pfx polymerase (Invitrogen)
- 37.7 ul dH2O

Thermal cycle in real-time thermal cycler according to the following protocol, but stop cycling before amplification yield plateaus (generally 8-12 cycles):

16. 95C for 5 min
17. 95C for 30 sec
18. 58C for 60 sec
19. 72C for 60 sec
20. goto 2, N more times

Prepare a shotgun next-generation sequencing library for analysis

- Purify desired amplicon population from non-specific amplification products by gel extraction.
- Concatemerize amplicons into high-molecular weight products suitable for shearing
- Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument. DNA should be sheared into fragments several hundred basepairs in length.
- Ligate adapters required for amplification by the sequencing platform used. If necessary, purify ligated product from unligated product and adapters.

Perform sequencing of library according to manufacturer's directions (e.g. Illumina,ABI, etc), reading the target sequence to determine abundance of the target nucleic acid.

Example 7: Use of MIPs, hybridization, and mutation-detection MIPs to genotype a set of 1000 targets

MIPs, hybridization, and mutation-detection MIPs are used to genotype a set of 1000 targets. The protocol permits detection of any of 50 specific known point mutations

First, separate MIP, hybridization, and mutation-detection MIP reactions are performed on a biological sample. A MIP capture reaction is performed essentially as described in Turner et al 2009, Nature methods 6:315-6. A set of MIPs is designed such that each probe in the set flanks one of the 1000 targets. Separately, a hybridization enrichment reaction is performed using the Agilent SureSelect procedure. Prior to selection, the genomic DNA to be enriched is converted into a shotgun sequencing library using Illumina's 'Fragment Library' kit and protocol. Agilent's web interface is used to design a set of probes which will hybridize to the target nucleic acids. Separately, a set of probes are designed (mutation-detection MIPs) which will form MIPs only if mutations (e.g., specific polymorphisms) are present. Each mutation-detection MIP has a 3'-most base identity that is specific for a single known mutation. A reaction with this set of mutation-detection MIPs is performed to selectively detect the presence of any mutant alleles.

Once all three reactions have been performed, the two MIP reactions are combined (e.g., at potentially non-equimolar ratios to further increase sensitivity of mutation detection) into a single tube, and run as one sample on the next-generation DNA sequencing instrument. The hybridization-enriched reaction is run as a separate sample on the next-generation DNA sequencing instrument. Reads from each 'sample' are combined by a software algorithm which forms a consensus diploid genotype at each position in the target set by evaluating the total coverage at each position, the origin of each read in that total coverage, the quality score of each individual read, and the presence (or absence) of any reads derived from mutation-specific MIPs overlapping the region.

It should be appreciated that the preceding examples are non-limiting and aspects of the invention may be implemented as described herein using alternative techniques and/or protocols that are available to one or ordinary skill in the art.

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It will be clear that the methods may be practiced other than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present disclosure are possible in light of the above teachings and, therefore, are within the scope of the claims. Preferred features of each aspect of the disclosure are as for each of the other aspects mutatis mutandis. The documents including patents, patent applications, journal articles, or other disclosures mentioned herein are hereby incorporated by reference in their entirety. In the event of conflict, the disclosure of present application controls, other than in the event of clear error.

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CLAIMS

What is claimed is:

1. A method of analyzing a plurality of genetic loci, the method comprising:
contacting each of a plurality of target nucleic acids with a probe set,
wherein each probe set comprises a plurality of different probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids flanking the same strand of one of a plurality of subregions of the target nucleic acid, wherein the subregions of the target nucleic acid are different, and wherein each subregion overlaps with at least one other subregion,
isolating a plurality of nucleic acids each having a nucleic acid sequence of a different subregion for each of the plurality of target nucleic acids, and
analyzing the isolated nucleic acids.

2. The method of claim 1, wherein at least one subregion entirely overlaps at least one other subregion.

3. The method of claim 1, wherein the sequences of the 5' region and the 3' region of each probe are, respectively, non-overlapping with the sequences of the 5' region and the 3' region of each other probe.

4. The method of claim 1, wherein the sequences of the 5' region and the 3' region of each probe are, respectively, different than the sequences of the 5' region and the 3' region of each other probe.

5. A method of analyzing a plurality of genetic loci, the method comprising:
contacting each of a plurality of target nucleic acids with a probe set,
wherein each probe set comprises a plurality of different probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids flanking the same strand of one of a plurality of subregions of the target nucleic acid, wherein the subregions of the target nucleic acid are different, and wherein a portion of the 5' region and a portion of the 3' region of a probe have, respectively, the sequence of the 5' region and the 3' region of a different probe,

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isolating a plurality of nucleic acids each having a nucleic acid sequence of a different subregion for each of the plurality of target nucleic acids, and

analyzing the isolated nucleic acids.

6. The method of claim 1 or 5, wherein the target nucleic acids are selected from Table 1.

7. The method of claim 1 or 5, wherein the analyzing comprises genotyping a polymorphism of the target nucleic acid.

8. The method of claim 7, wherein the polymorphism is selected from Table 2.

9. A method of genotyping a subject, the method comprising:

determining the sequence of at least a threshold number of independently isolated nucleic acids, wherein the sequence of each isolated nucleic acid comprises a target nucleic acid sequence and a differentiator tag sequence,

wherein the threshold number is a number of unique combinations of target nucleic acid and differentiator tag sequences, wherein the isolated nucleic acids are identified as independently isolated if they comprise unique combinations of target nucleic acid and differentiator tag sequences, and wherein the target nucleic acid sequence is the sequence of a genomic locus of a subject.

10. The method of claim 9., wherein the isolated nucleic acids are molecular inversion probe capture products.

11. A method of genotyping a subject, the method comprising:

determining the sequence of molecular inversion probe capture products, each comprising a molecular inversion probe and a target nucleic acid, wherein the sequence of the molecular inversion probe comprises a differentiator tag sequence and, optionally, a primer sequence, and wherein the target nucleic acid is a captured genomic locus of a subject, and

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genotyping the subject at the captured genomic locus based on the sequence of at least a threshold number of unique combinations of target nucleic acid and differentiator tag sequences of molecular inversion probe capture products.

12. A method of genotyping a subject, the method comprising:

obtaining molecular inversion probe capture products, each comprising a molecular inversion probe and a target nucleic acid, wherein the sequence of the molecular inversion probe comprises a differentiator tag sequence and, optionally, a primer sequence, wherein the target nucleic acid is a captured genomic locus of the subject,

amplifying the molecular inversion probe capture products, and

genotyping the subject by determining, for each target nucleic acid, the sequence of at least a threshold number of unique combinations of target nucleic acid and differentiator tag sequence of molecular inversion probe capture products.

13. The method of claim 12, wherein the obtaining comprises capturing target nucleic acids from a genomic sample of the subject with molecular inversion probes, each comprising a unique differentiator tag sequence.

14. The method of claim 12 or 13, wherein the capturing is performed under conditions wherein the likelihood of obtaining two or more molecular inversion probe capture products with identical combinations of target and differentiator tag sequences is equal to or less than a predetermined value, optionally wherein the predetermined value is about 0.05.

15. The method of any one of claims 12-14, wherein the threshold number for a specific target nucleic acid sequence is selected based on a desired statistical confidence for the genotype.

16. The method of any one of claims 12-14, further comprising determining a statistical confidence for the genotype based on the number of unique combinations of target nucleic acid and differentiator tag sequences.

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17. A method of analyzing a plurality of genetic loci, the method comprising:

obtaining a plurality of molecular inversion probe capture products each comprising a molecular inversion probe and a target nucleic acid, wherein the sequence of the molecular inversion probe comprises a differentiator tag sequence and, optionally, a primer sequence,

amplifying the plurality of molecular inversion probe capture products,

determining numbers of occurrence of combinations of target nucleic acid and differentiator tag sequence of molecular inversion probe capture products in the amplified plurality, and

if the number of occurrence of a specific combination of target nucleic acid sequence and differentiator tag sequence exceeds a predetermined value, detecting bias in the amplification of the molecular inversion probe comprising the specific combination.

18. The method of claim 17, further comprising genotyping target sequences in the plurality, wherein the genotyping comprises correcting for bias, if detected.

19. The method of any of claims 9-18, wherein the target nucleic acid sequence is

a sequence of a gene selected from Table 1.

20. A method for determining whether a target nucleic acid has an abnormal length, the method comprising evaluating the capture efficiency of a target nucleic acid in a biological sample from a subject, wherein a capture efficiency that is different from a reference capture efficiency is indicative of the presence, in the biological sample, of a target nucleic acid having an abnormal length.

21. The method of claim 20, comprising determining the capture efficiency of a target region suspected of having a deletion or insertion and comparing the capture efficiency to a reference indicative of a normal capture efficiency.

22. The method of claim 20-21, wherein the capture efficiency is lower than the reference capture efficiency.

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23. The method of claim 22, wherein the subject is identified as having an insertion in the target region.

24. The method of claim 20-21, wherein the capture efficiency is higher than the reference capture efficiency.

25. The method of claim 24, wherein the subject is identified as having a deletion in the target region.

26. The method of claim 23, wherein the subject is identified as being heterozygous for the insertion.

27. The method of claim 25, wherein the subject is identified as being heterozygous for the deletion.

28. The method of any prior claim, wherein a sub-target nucleic acid is captured from the target nucleic acid using a molecular inversion probe.

29. The method of claim 28, wherein the molecular inversion probe comprises a first targeting arm at its 5' end and a second targeting arm at its 3' end, wherein the first targeting arm is capable of specifically hybridizing to a first region flanking one end of the sub-target nucleic acid, and wherein the second targeting arm is capable of specifically hybridizing to a second region flanking the other end of the sub-target nucleic acid on the same strand of the target nucleic acid.

30. The method of claim 29, wherein the first and second targeting arms are between about 10 and about 100 nucleotides long.

31. The method of claim 30, wherein the first and second targeting arms are about 10-20, 20-30, 30-40, or 40-50 nucleotides long.

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32. The method of claim 31, wherein the first and second targeting arms are about 20 nucleotides long.

33. The method of any one of claims 29-31, wherein the first and second targeting arms have the same length.

34. The method of any one of claims 29-33, wherein the hybridization Tms of the first and second targeting arms are similar.

35. The method of claim 34, wherein the hybridization Tms of the first and second targeting arms are within 2-5 C of each other.

36. The method of claim 34, wherein the hybridization Tms of the first and second targeting arms are identical.

37. The method of any one of claims 28-36, wherein the sub-target nucleic acid contains a nucleic acid repeat.

38. The method of claim 37, wherein the nucleic acid repeat is a dinucleotide or trinucleotide repeat.

39. The method of claim 37, wherein the sub-target nucleic acid contains 10-100 copies of the nucleic acid repeat in the absence of an abnormal increase or decrease in nucleic acid repeats.

40. The method of claim 37, wherein the sub-target nucleic acid is a region of the Fragile-X locus that contains a nucleic acid repeat.

41. The method of any one of claims 29-36, wherein one or both targeting arms hybridize to a region on the target nucleic acid that is immediately adjacent to a region of nucleic acid repeats.

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42. The method of any one of claims 29-36, wherein one or both targeting arms hybridize to a region on the target nucleic acid that is separated from a region of nucleic acid repeats by a region that does not contain any nucleic acid repeats.

43. The method of any one of claims 29-36, wherein the molecular inversion probe further comprises a primer-binding region that can be used to sequence the captured sub-target nucleic acid and optionally the first and/or second targeting arm.

44. The method of any of the prior claims, wherein a plurality of different target nucleic acids are analyzed in a biological sample.

45. The method of claim 44, wherein the plurality of target nucleic acids are analyzed using a plurality of different molecular inversion probes.

46. The method of claim 45, wherein each different molecular inversion probe comprises a different pair of first and second targeting arms at each of the 3' and 5' ends.

47. The method of claim 46, wherein each different molecular inversion probe comprises the same primer-binding sequence.

48. The method of any prior claim, wherein the biological sample is a blood sample.

49. The method of any prior claim, wherein the biological sample is a tissue sample.

50. The method of any prior claim, wherein the capture efficiency is evaluated by determining an amount of target nucleic acid that is captured.

51. The method of claim 50, wherein the amount of target nucleic acid that is captured is determined by determining a number of independently captured target nucleic acid molecules.

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52. The method of claim 50-51, wherein the amount of target nucleic acid that is captured is compared to a reference amount of captured nucleic acid.

53. The method of claim 52, wherein the reference amount is determined by determining a number of independently captured molecules of a reference nucleic acid.

54. The method of claim 53, wherein the reference nucleic acid is a nucleic acid of a different locus in the biological sample that is not suspected of containing a deletion or insertion.

55. The method of claim 53, wherein the reference nucleic acid is a nucleic acid of known size and amount that is added to the capture reaction.

56. The method of any prior claim, wherein a subject is identified as having an insertion or deletion in one or more alleles of the genetic locus if the capture efficiency is statistically significantly different that the reference capture efficiency.

57. A method for estimating the length of a target nucleic acid, the method comprising:

(i) contacting the target nucleic acid with a plurality of detection probes under conditions that permit hybridization of the detection probes to the target nucleic acid,

wherein each detection probe is a polynucleotide that comprises a first arm that hybridizes to a first region of the target nucleic acid and a second arm that hybridizes to a second region of the target nucleic acid,

wherein the first and second regions are on a common strand of the target nucleic acid, and

wherein the nucleotide sequence between the 5' end of the first region and the 3' end of the second region is the nucleotide sequence of a sub-target nucleic acid; and

(ii) capturing a plurality of sub-target nucleic acids that are hybridized with the plurality of detection probes; and

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(iii) measuring the frequency of occurrence of a sub-target nucleic acid in the plurality of sub-target nucleic acids, wherein the frequency of occurrence of the sub-target nucleic acid in the plurality of sub-target nucleic acids is indicative of the length of the sub-target nucleic acid.

58. A method of increasing the sensitivity of a nucleic acid detection assay, the method comprising:

obtaining a first preparation of a target nucleic acid using a first preparative method on a biological sample,

obtaining a second preparation of a target nucleic acid using a second preparative method on the biological sample,

assaying the sequences obtained in both first and second nucleic acid preparations,

using the sequence information from both first and second nucleic acid preparations to determine the genotype of the target nucleic acid in the biological sample, wherein the first and second preparative methods have different systematic sequence biases.

59. The method of claim 58, wherein the first and second nucleic acid preparations are combined prior to performing a sequence assay.

60. The method of claim 58, wherein separate sequence assays are performed on the first and second nucleic acid preparations and the sequence information from both assays are combined to determine the genotype of the target nucleic acid in the biological sample.

61. The method of claim 58, wherein the first preparative method is a PCR-based, a hybridization-based, or a circular probe-based preparative method.

62. The method of claim 61, wherein the second preparative method is a PCR-based, a hybridization-based, or a circular probe-based preparative method, provided that the second method is different from the first method.

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63. A method of obtaining a nucleic acid preparation that is representative of the nucleic acid in a biological sample, the method comprising

obtaining a first nucleic acid preparation using a first preparative method on a biological sample,

obtaining a second nucleic acid preparation using a second preparative method on the biological sample, and

combining the first and second nucleic acid preparations to obtain a combined preparation that is representative of nucleic acid in the biological sample.

64. The method of claim 1 or 6, further comprising performing a third nucleic acid preparation using a third preparative method that is different from the first and second preparative methods, wherein the first, second, and third preparative methods all have different systematic sequence biases.

65. The method of claim any of the prior claims, wherein the different preparative methods are used for a plurality of different loci in the biological sample to increase the sensitivity of a multiplex nucleic acid analysis.

66. A method of genotyping a nucleic acid in a biological sample, the method comprising:

obtaining a nucleic acid preparation using a preparative method on a biological sample,

sequencing a target nucleic acid of the nucleic acid preparation,

and performing a molecular inversion probe capture reaction on the biological sample, wherein a molecular inversion probe capture of the target nucleic acid in the biological sample is indicative of the presence of a polymorphism in the target nucleic acid,

genotyping the target nucleic acid based on the results of the sequencing and the capture reaction.

67. The method of any of the prior claims, wherein the target nucleic acid has a sequence of a gene selected from Table 1.

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ABSTRACT

Aspects of the invention relates to methods and compositions that are useful to reduce bias and increase the reproducibility of multiplex analysis of genetic loci. In some configurations, predetermined preparative steps and/or nucleic acid sequence analysis techniques are used in multiplex analyses for a plurality of genetic loci in a plurality of samples.

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FIG. 1

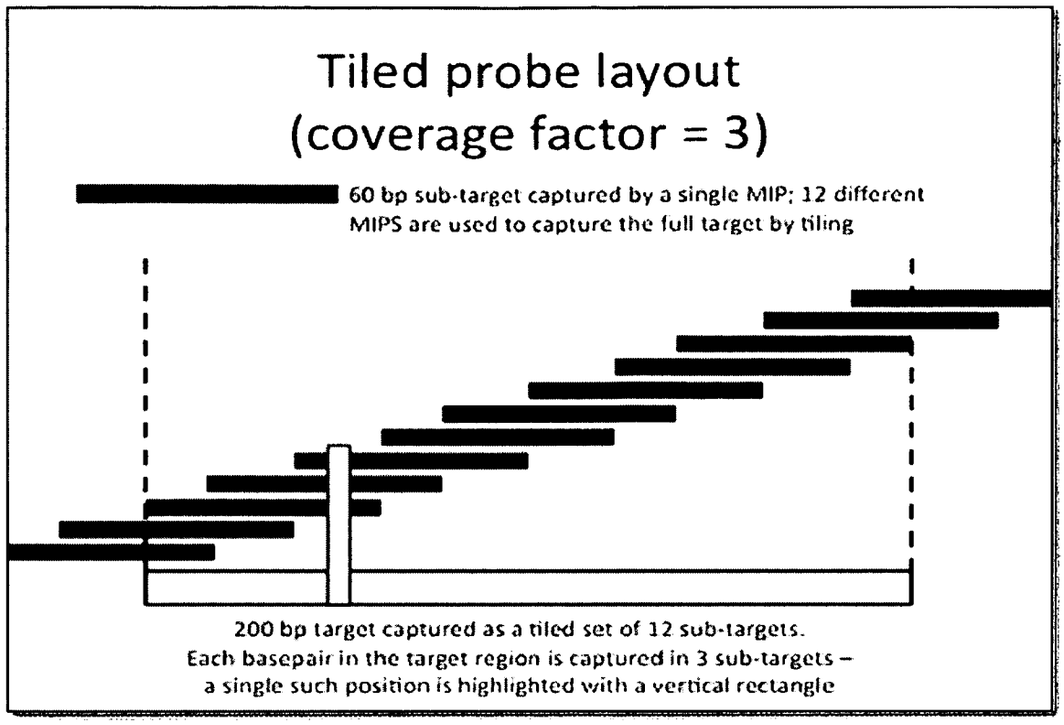

Tiled probe layout
(coverage factor = 3)
60 bp sub-target captured by a single MIP; 12 different MIPS are used to capture the full target by tiling
200 bp target captured as a tiled set of 12 sub-targets.
Each basepair in the target region is captured in 3 sub-targets –
a single such position is highlighted with a vertical rectangle

FIG. 2

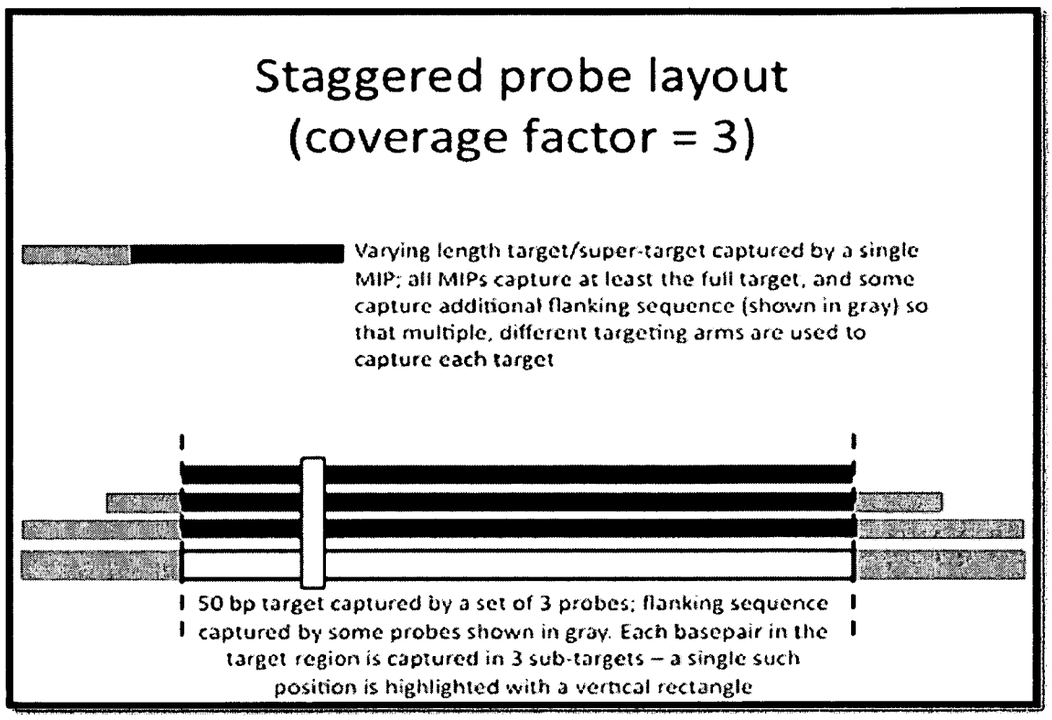

Staggered probe layout
(coverage factor = 3)
Varying length target/super-target captured by a single MIP; all MIPs capture at least the full target, and some capture additional flanking sequence (shown in gray) so that multiple, different targeting arms are used to capture each target
50 bp target captured by a set of 3 probes; flanking sequence captured by some probes shown in gray. Each basepair in the target region is captured in 3 sub-targets – a single such position is highlighted with a vertical rectangle

FIG. 3

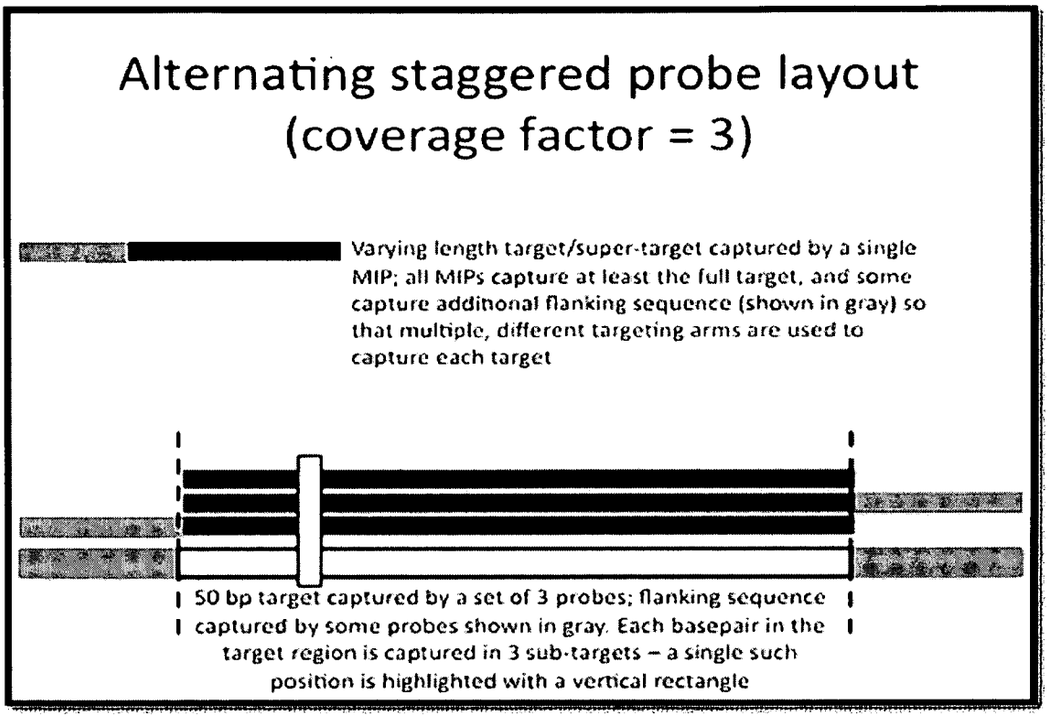

Alternating staggered probe layout
(coverage factor = 3)
Varying length target/super-target captured by a single MIP; all MIPs capture at least the full target, and some capture additional flanking sequence (shown in gray) so that multiple, different targeting arms are used to capture each target
50 bp target captured by a set of 3 probes; flanking sequence captured by some probes shown in gray. Each basepair in the target region is captured in 3 sub-targets – a single such position is highlighted with a vertical rectangle

FIG. 4

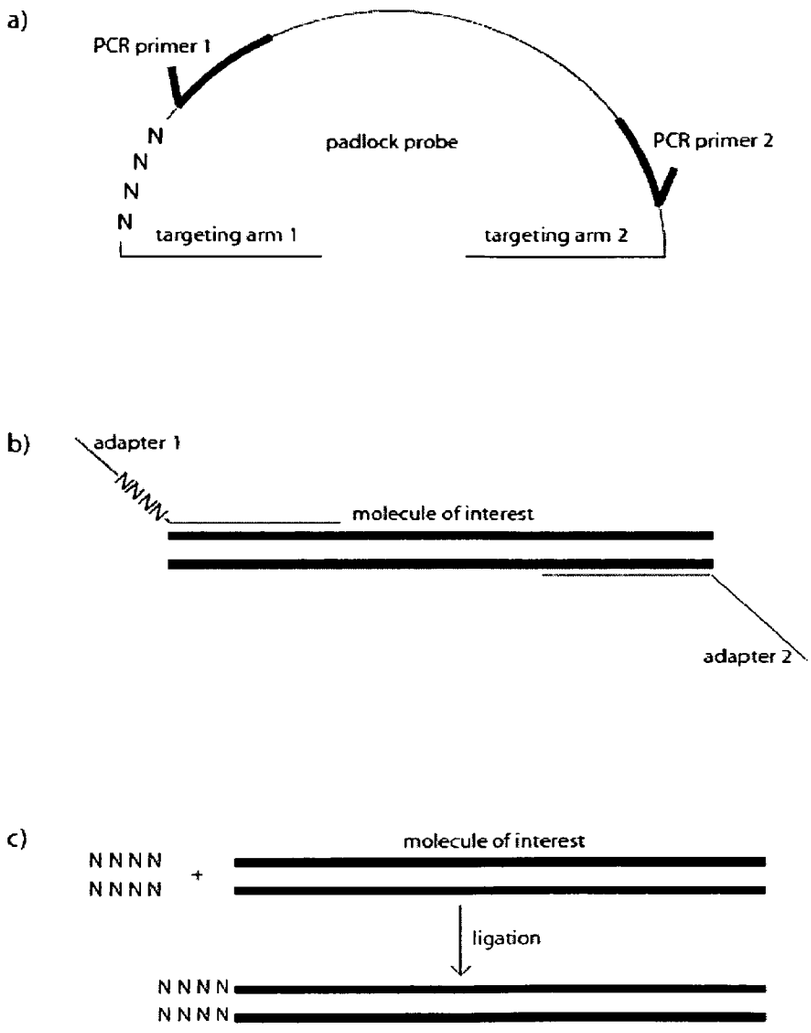

a)
PCR primer 1
N
N
N
N
padlock probe
PCR primer 2
targeting arm 1
targeting arm 2
b)
adapter 1
NNNN
molecule of interest
adapter 2
c)
NNNN
NNNN
+
molecule of interest
ligation
NNNN
NNNN

FIG. 5

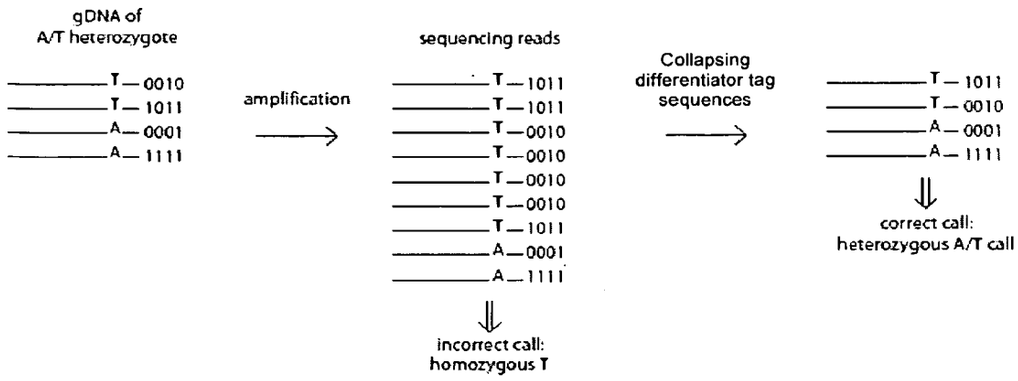

gDNA of
A/T heterozygote
T — 0010
T — 1011
A — 0001
A — 1111
amplification
sequencing reads
T — 1011
T — 1011
T — 0010
T — 0010
T — 0010
T — 0010
T — 1011
A — 0001
A — 1111
incorrect call:
homozygous T
Collapsing
differentiator tag
sequences
T — 1011
T — 0010
A — 0001
A — 1111
correct call:
heterozygous A/T call

FIG. 6

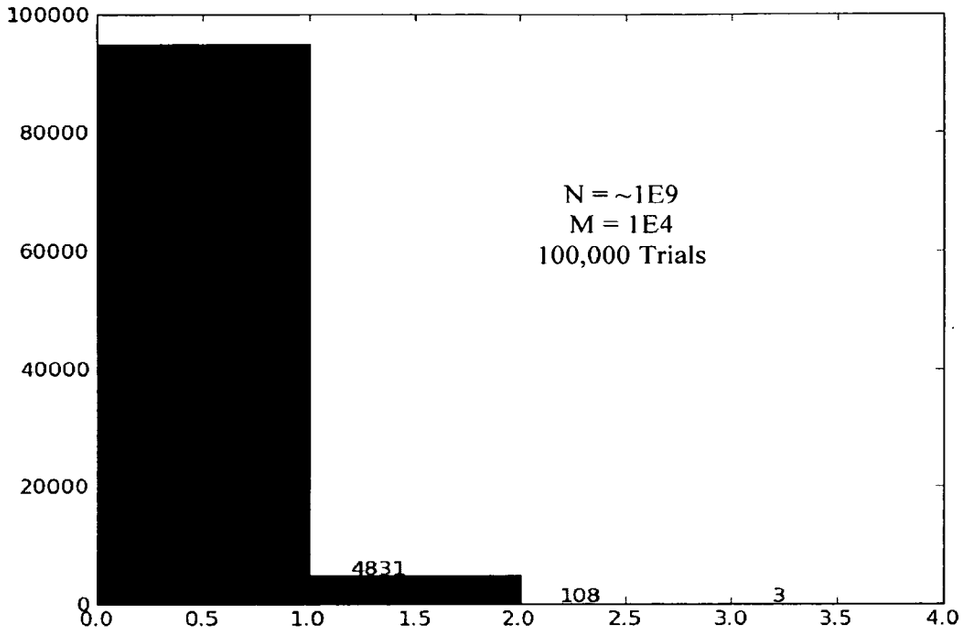

100000
80000
60000
40000
20000
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
N = ~1E9
M = 1E4
100,000 Trials
4831
108
3
Independent Occurrences of
Target:Differentiator Tag Sequence
100,000 Trials

FIG. 7

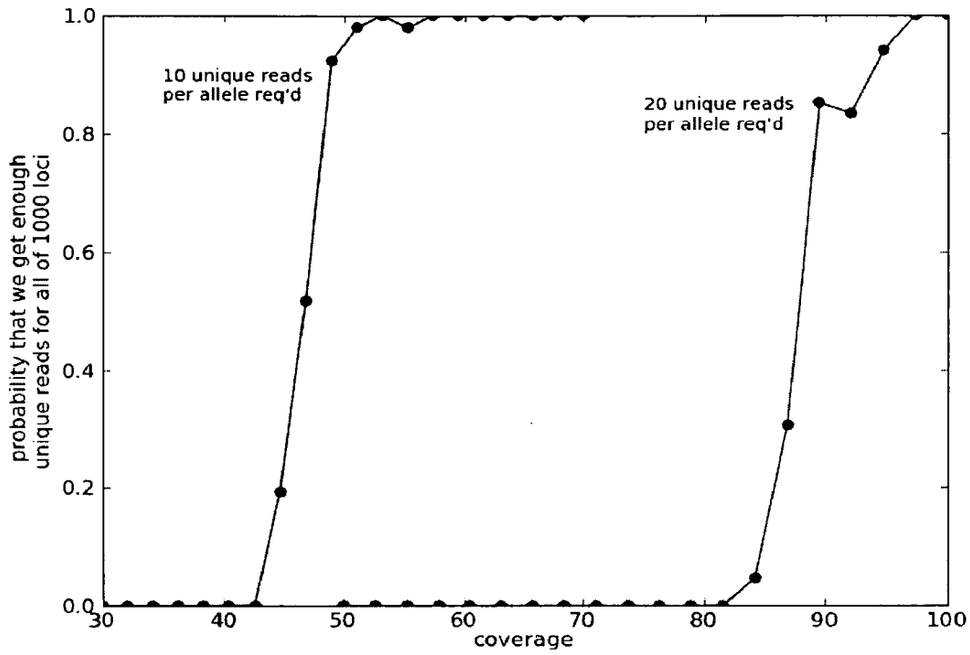

1.0
0.8
0.6
0.4
0.2
0.0
probability that we get enough unique reads for all of 1000 loci
10 unique reads per allele req'd
20 unique reads per allele req'd
30
40
50
60
70
80
90
100
coverage

FIG. 8

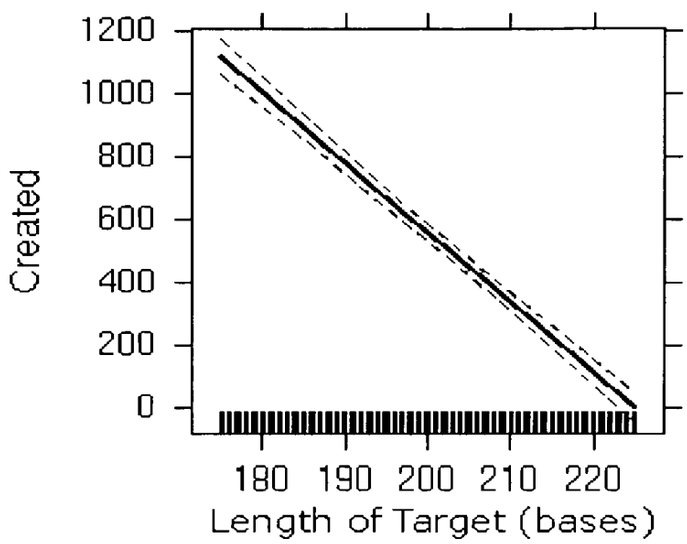

1200
1000
800
600
400
200
0
Created
180
190
200
210
220
Length of Target (bases)

FIG. 9

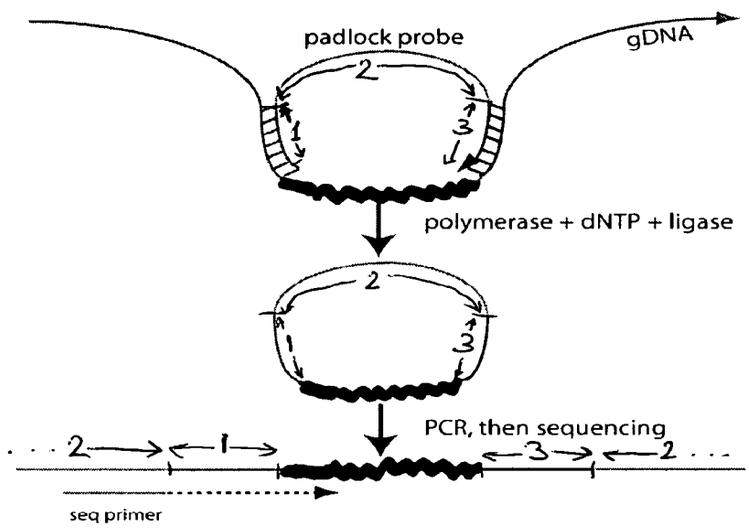

padlock probe
gDNA
2
1
3
polymerase + dNTP + ligase
2
1
3
PCR, then sequencing
2
1
3
2
seq primer

FIG. 10

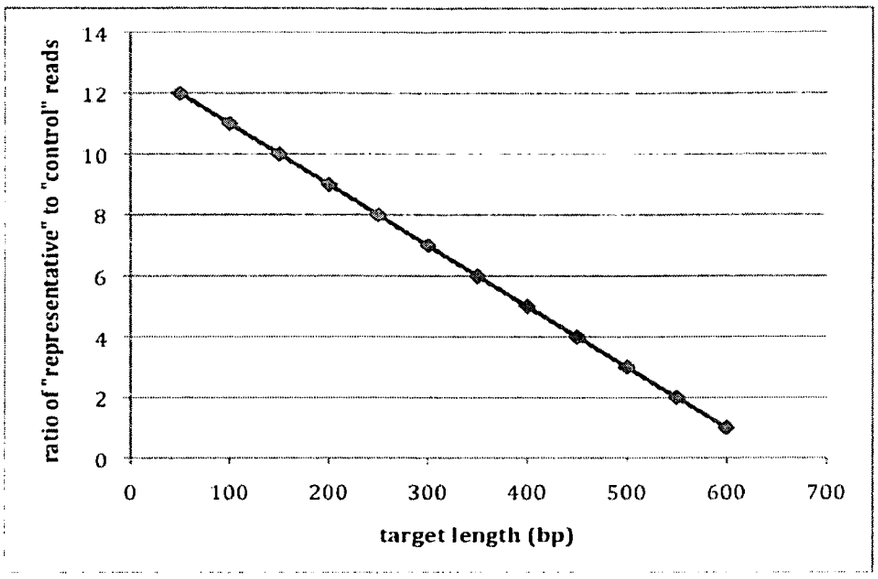

ratio of "representative" to "control" reads
14
12
10
8
6
4
2
0
0
100
200
300
400
500
600
700
target length (bp)

FIG. 11

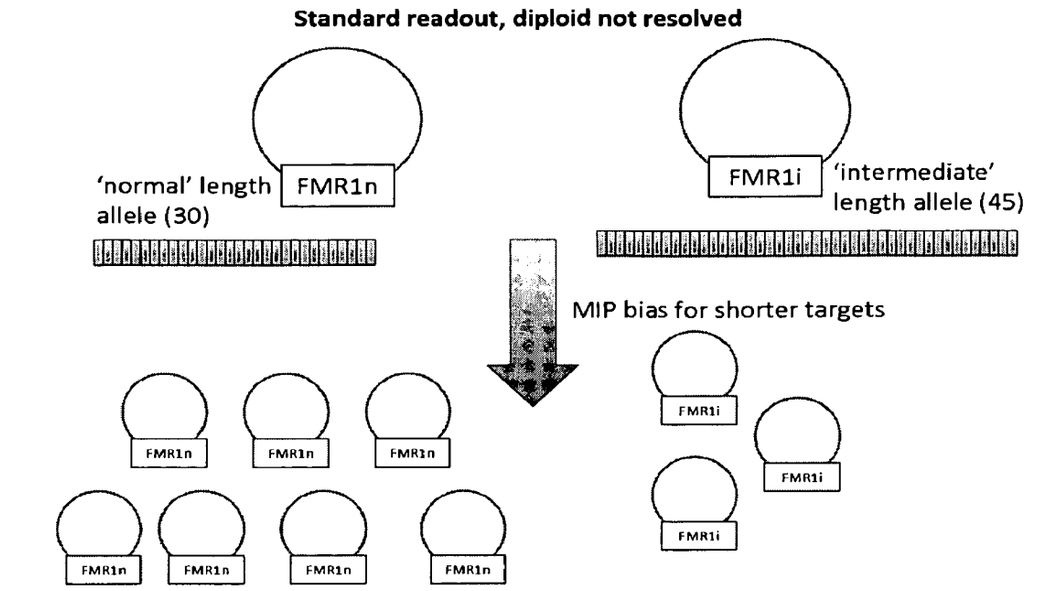

Standard readout, diploid not resolved
'normal' length allele (30)
FMR1n
FMR1i
'intermediate' length allele (45)
MIP bias for shorter targets
FMR1n
FMR1n
FMR1n
FMR1n
FMR1n
FMR1n
FMR1n
FMR1i
FMR1i
FMR1i
Readout: sum of alleles appears as 'long' end of normal length range, not intermediate het

FIG. 11B

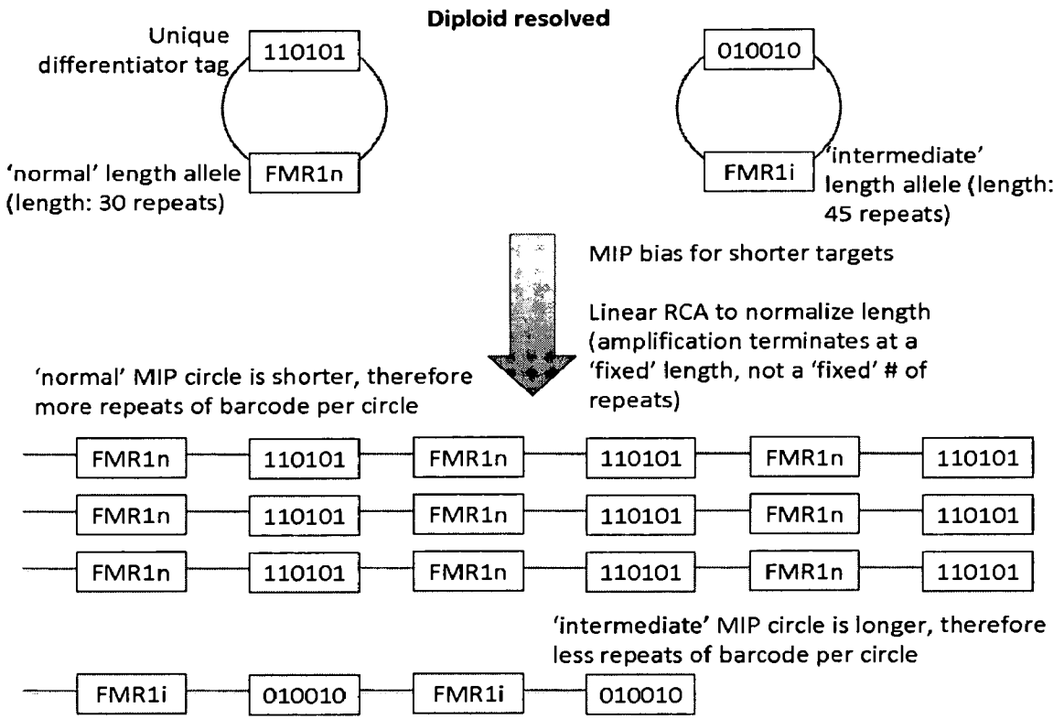

Diploid resolved
Unique differentiator tag
110101
FMR1n
'normal' length allele (length: 30 repeats)
010010
FMR1i
'intermediate' length allele (length: 45 repeats)
MIP bias for shorter targets
Linear RCA to normalize length (amplification terminates at a 'fixed' length, not a 'fixed' # of repeats)
'normal' MIP circle is shorter, therefore more repeats of barcode per circle
FMR1n
110101
'intermediate' MIP circle is longer, therefore less repeats of barcode per circle
FMR1i
010010

FIG. 11C

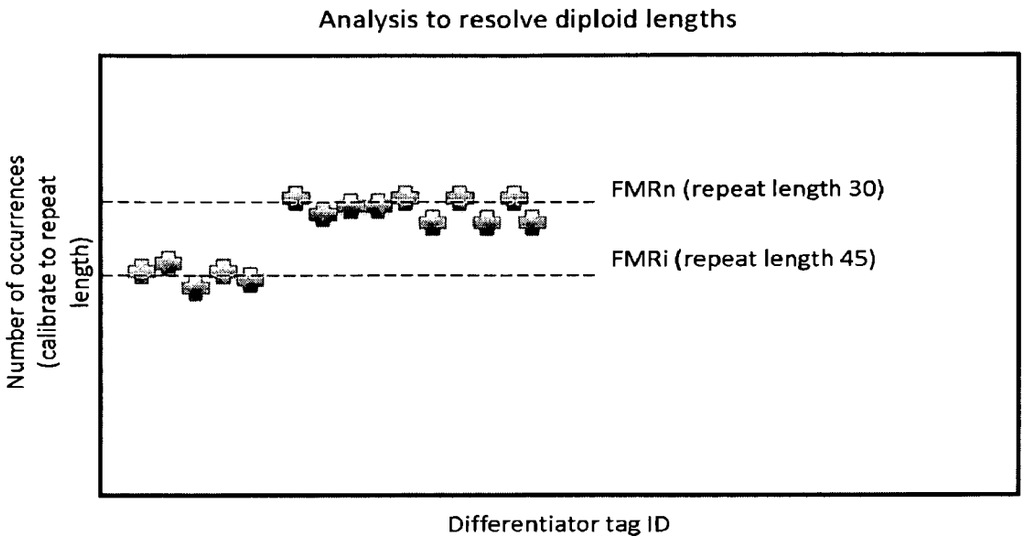

Analysis to resolve diploid lengths
Number of occurrences (calibrate to repeat length)
FMRn (repeat length 30)
FMRi (repeat length 45)
Differentiator tag ID

FIG. 12

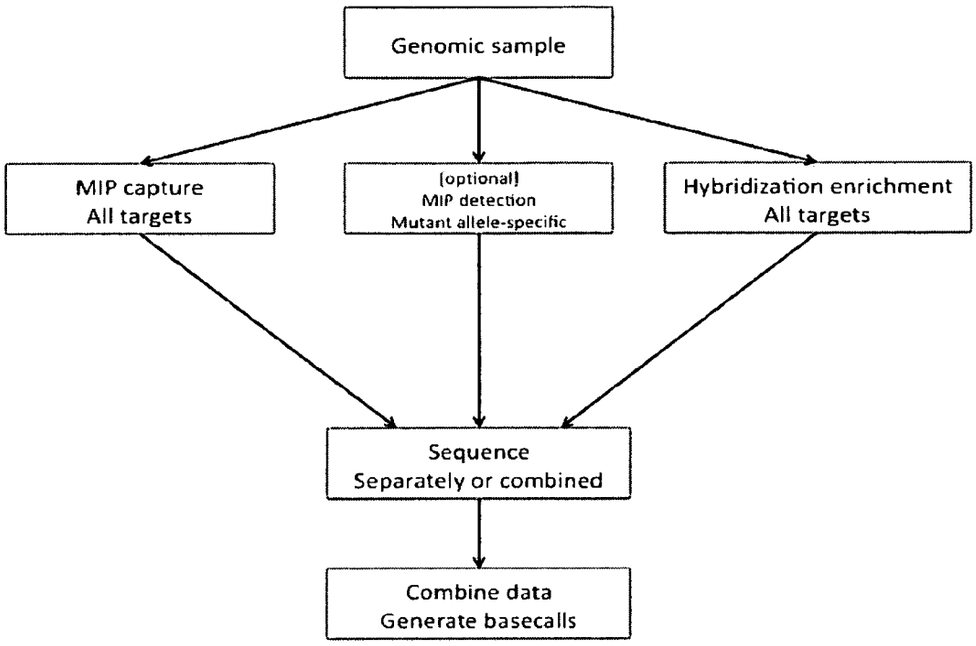

Genomic sample
MIP capture
All targets
(optional)
MIP detection
Mutant allele-specific
Hybridization enrichment
All targets
Sequence
Separately or combined
Combine data
Generate basecalls

FIG. 13

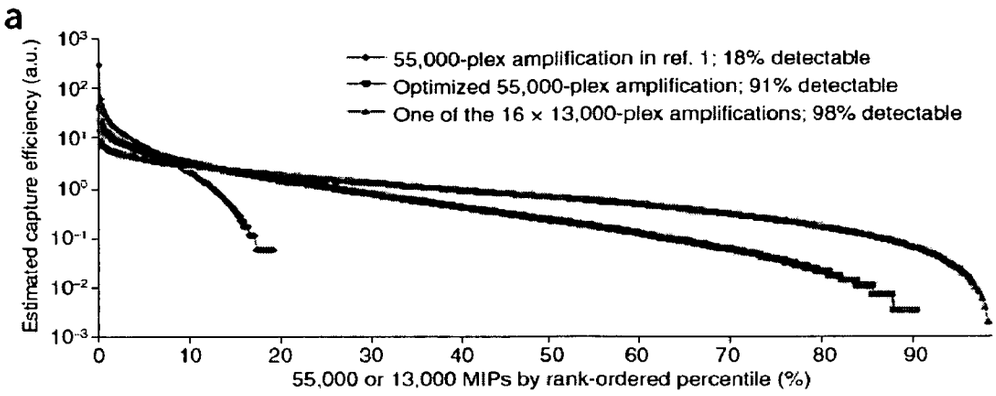
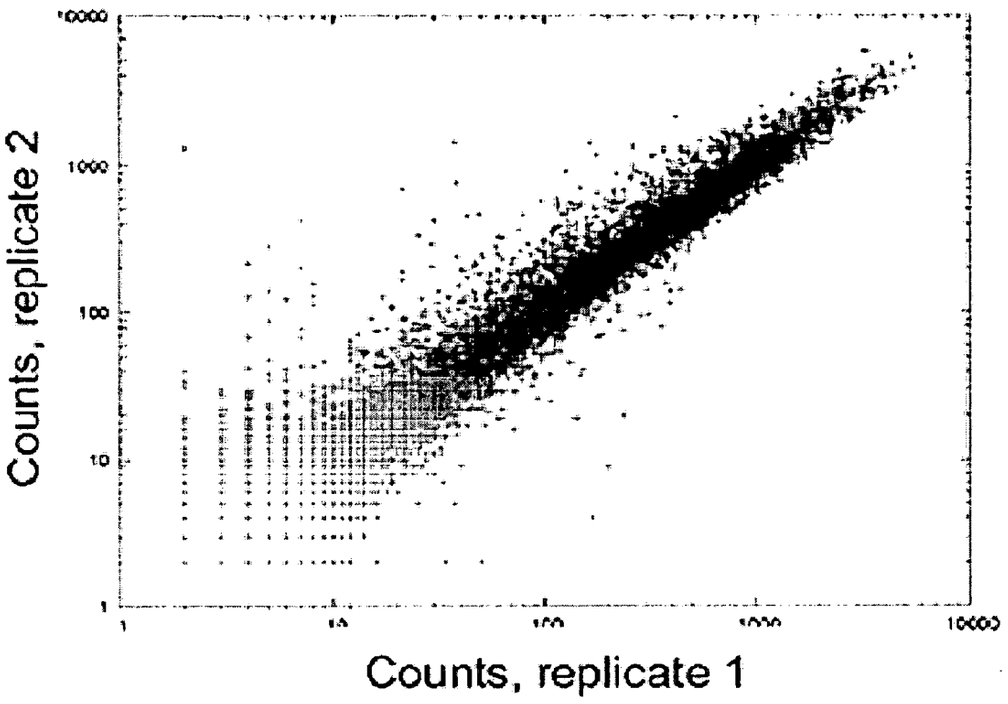

a
Estimated capture efficiency (a.u.)
10³
10²
10¹
10⁰
10⁻¹
10⁻²
10⁻³
0
10
20
30
40
50
60
70
80
90
55,000 or 13,000 MIPs by rank-ordered percentile (%)
55,000-plex amplification in ref. 1; 18% detectable
Optimized 55,000-plex amplification; 91% detectable
One of the 16 × 13,000-plex amplifications; 98% detectable

FIG. 14


Counts, replicate 2
Counts, replicate 1
10000
1000
100
10
1
1
10000

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	GSGE-002/04US 29258/78
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
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Residence Information (Select One) ● US Residency Non US Residency Active US Military Service

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State/Province	MA
Postal Code	02138
Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Uri		Laserson	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

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State/Province	MA
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Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

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For further information see 37 CFR 1.33(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	GSGE-002/04US 29258/78
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

☐ **An Address is being provided for the correspondence Information of this application.**

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Application Information:

Title of the Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS		
Attorney Docket Number	GSGE-002/04US 29258/78	**Small Entity Status Claimed** ☒	
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	16	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☒ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	21710		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	GSGE-002/04US 29258/78
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	13/266862	2012-03-13
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13/266862	a 371 of international	PCT/US2010/001293	2010-04-30
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2010/001293	Claims benefit of provisional	61/182089	2009-05-28
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2010/001293	Claims benefit of provisional	61/179358	2009-05-18
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2010/001293	Claims benefit of provisional	61/178923	2009-05-15
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US2010/001293	Claims benefit of provisional	61/174470	2009-04-30

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	GSGE-002/04US 29258/78
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	GSGE-002/04US 29258/78
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	GSGE-002/04US 29258/78
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Good Start Genetics, Inc.		
Mailing Address Information For Applicant:			
Address 1	237 Putnam Avenue		
Address 2			
City	Cambridge	**State/Province**	MA
Country	US	Postal Code	02139
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	GSGE-002/04US 29258/78
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Thomas C. Meyers/			Date (YYYY-MM-DD)	2016-08-08
First Name	Thomas	Last Name	Meyers	Registration Number	36,989

Additional Signature may be generated within this form by selecting the Add button. Add

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	GSGE-002/04US 29258/78
	Application Number	
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Matthew York
Attorney Docket Number:	GSGE-002/04US 29258/78

Filed as Small Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2800**

Electronic Acknowledgement Receipt

EFS ID:	26610830
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Denise Garrido
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	11-AUG-2016
Filing Date:	
Time Stamp:	11:56:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	GSGE-002-04US_IDS_Transmittal.pdf	19539 bc6bc610484d90c550120791520476d4f4d00ac9	no	1

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	GSGE-002_04US_IDS_1.pdf	1044601 7fd6d4eb77d04e132696eb28d5b1a58e3dd9ed28	no	28
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	GSGE-002_04US_IDS_2.pdf	1038421 5875bc0852df10544ea8f9761c6451127354a19b	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
4	Information Disclosure Statement (IDS) Form (SB08)	GSGE-002_04US_IDS_3.pdf	1039183 a0dc2d71b73958c6163b76f9de09cd07c18e2065	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
5	Information Disclosure Statement (IDS) Form (SB08)	GSGE-002_04US_IDS_4.pdf	1038447 ab2b7d30fcdb47992bc978775cf6e0e63ce099ad	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
6	Non Patent Literature	Miner_Nucl-Acids-Res-2004.pdf	198570 55b56ce20725e4b1fd5f54e33f363f7d840e518c	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	4378761		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket No.: GSGE-002/04US 29258/78

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	NOT YET ASSIGNED
TITLE:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT (IDS)

Applicant submits herewith an IDS. Some information cited in the IDS has previously been cited by or submitted to the Office in a prior application (U.S. Application No. 13/266,862) that is relied on for an earlier filing date under 35 U.S.C. 120 and is now listed on the IDS as U.S. Publication No. 2012/0165202. Accordingly, applicant believes that copies of some information listed on the IDS need not be provided. *See 37 CFR 1.98(d)*; *M.P.E.P. 609.04(a)(II)(D)*.

Applicant believes that no fees are required to have the IDS entered but nevertheless authorizes any required fee to be charged to deposit account no. 500369.

Dated: August 11, 2016

Respectfully submitted,
BROWN RUDNICK LLP

/Thomas C. Meyers/
Thomas C. Meyers Reg. No. 36,989
Attorney for Applicant
Email: tmeyers@brownrudnick.com

BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
Tel: 617-856-8483
Fax: 617-856-8201

62537615-029258/0078

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2016-08-11
Name/Print	Thomas C. Meyers	Registration Number	36,989

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4683195		1987-07-28	Mullis et al.	
	2	4683202		1987-07-28	Mullis	
	3	4988617		1991-01-29	Landegren et al.	
	4	5234809		1993-08-10	Boom et al.	
	5	5242794		1993-09-07	Whiteley et al.	
	6	5494810		1996-02-27	Barany et al.	
	7	5583024		1996-12-10	McElroy (deceased), et al.	
	8	5604097		1997-02-18	Brenner	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

	9	5636400		1997-06-10	Young	
	10	5674713		1997-10-07	McElroy (deceased), et al.	
	11	5695934		1997-12-09	Brenner	
	12	5700673		1997-12-23	McElroy (deceased), et al.	
	13	5701256		1997-12-23	Marr et al.	
	14	5830064		1998-11-03	Bradish et al.	
	15	5846719		1998-12-08	Brenner et al.	
	16	5863722		1999-01-26	Brenner	
	17	5866337		1999-02-02	Schon	
	18	5869252		1999-02-09	Bouma et al.	
	19	5871921		1999-02-16	Landegren et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

	20	5993611		1999-11-30	Moroney, III et al.	
	21	6100099		2000-08-08	Gordon et al.	
	22	6138077		2000-10-24	Brenner	
	23	6150516		2000-11-21	Brenner et al.	
	24	6172214		2001-01-09	Brenner	
	25	6172218		2001-01-09	Brenner	
	26	6197508		2001-03-06	Stanley	
	27	6210891		2001-04-03	Nyren et al.	
	28	6223128		2001-04-24	Allex et al.	
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	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
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15/231,687	08/08/2016	1634	730	GSGE-002/04US 29258/78	11	1

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Inventor(s)

Gregory Porreca, Cambridge, MA;
Uri Laserson, Boston, MA;

Applicant(s)

Good Start Genetics, Inc., Cambridge, MA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/266,862 03/13/2012
which is a 371 of PCT/US10/01293 04/30/2010
which claims benefit of 61/182,089 05/28/2009
and claims benefit of 61/179,358 05/18/2009
and claims benefit of 61/178,923 05/15/2009
and claims benefit of 61/174,470 04/30/2009

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Petitioner Illumina, Inc., EX1003, p. 220

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/18/2016
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/231,687**
Projected Publication Date: Request for Non-Publication Acknowledged
Non-Publication Request: Yes
**********WARNING**********
Applicant has requested non-publication, certifying that the invention disclosed in this application has not been and will not be the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing; **and has also claimed** the benefit of an application filed in another country or under a multilateral agreement. Because the non-publication request and corresponding certification appears to be inconsistent with the priority claim, applicant is reminded that he/she has an obligation to promptly notify the Office and **rescind the non-publication request** if the invention disclosed in this application is the subject of an application filed in another country, or under a multilateral agreement, that requires eighteen-month publication.
**********WARNING**********
Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Petitioner Illumina, Inc., EX1003, p. 221

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Petitioner Illumina, Inc., EX1003, p. 223

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

FORMALITIES LETTER

OC000000085263918

Date Mailed: 08/23/2016

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The application contains drawings and the specification contains a brief description of the drawings. However, the specification does not contain a brief description of the several views of the drawings as required by 37 CFR 1.74 and 37 CFR 1.77(b)(7) and/or a drawing(s) has not been labeled in accordance with 37 CFR 1.84(u)(1). If each figure is not labeled "Fig." with a consecutive Arabic numeral (1, 2, etc.) or an Arabic numeral and capital letter in the English alphabet (A, B, etc.), then the drawing(s) must be relabeled in accordance with 37 CFR 1.84(u)(1). In addition, if the brief description of the several views of the drawings does not refer to the figure(s) as properly labeled, then the specification must be amended to correspond to the figure(s) as properly labeled and a substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required.
  - The drawings submitted to the Office are not electronically reproducible because portions of figures 14 are missing and/or blurry.
- This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c) Applicant must provide an initial paper or compact disc copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application** and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000).
- A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical

to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If applicant desires the sequence listing in the instant application to be identical with that of another application on file in the U.S. Patent and Trademark Office, such request in accordance with 37 CFR 1.821(e) may be submitted in lieu of a new CRF.

For questions regarding compliance to these requirements, please contact:

- **For Rules interpretation, call (571) 272-2510**
- **For CRF submission help, call (571) 272-2510**
- **For PatentIn software program support technical assistance, call (866)217-9197.**
- **Send e-mail correspondence for PatentIn software program help to ebc@uspto.gov**
- **Patent software is available at http://www.uspto.gov/patents/resources/tools/checker/patentinrel.jsp .**

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **70** surcharge.
- $(**0**) previous unapplied payment amount.
- $ **70** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Gregory Porreca
  Uri Laserson

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/tle/

Electronic Acknowledgement Receipt	
EFS ID:	27258164
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers
Filer Authorized By:	
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	21-OCT-2016
Filing Date:	08-AUG-2016
Time Stamp:	14:04:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$70
RAM confirmation Number	102416INTEFSW00000308500369
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Correspondence.pdf	161537 52772cbc633b7ad986f3d99f216a44259f4f91e4	no	3
Warnings:					
Information:					
2	CRF Statement Paper and CRF are the same	Statement_Seq_Listing.pdf	15307 1227ea093630966478e988ecb4fc32eb236f1bff	no	1
Warnings:					
Information:					
3	Drawings-only black and white line drawings	Replacement_Drawings.pdf	292753 343aaba3e0adf301b9fc142910626b81734486dc	no	16
Warnings:					
Information:					
4	Sequence Listing (Text File)	GSGE-002-04US-Sequence-Listing.txt	61754	no	-
Warnings:					
Information:					
5		Response.pdf	23987 f8d89b1d912256b618a642565689d1b5eac89c89	yes	3

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Response to Pre-Exam Formalities Notice	1	1
Specification	2	2
Applicant Arguments/Remarks Made in an Amendment	3	3

Warnings:					
Information:					
6	Sequence Listing	Sequence_Listing.pdf	73579 aa711da9d41b5f04dff664bb914ccd62bdb45d84	no	42
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	30369 13329f8c800cf05949d8c66d4d4187812933c5fb	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	659286		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

ENTERED IN CPI

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

FORMALITIES LETTER

Date Mailed: 08/23/2016

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

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  - The drawings submitted to the Office are not electronically reproducible because portions of figures 14 are missing and/or blurry.
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- A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical

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- **For CRF submission help, call (571) 272-2510**
- **For PatentIn software program support technical assistance, call (866)217-9197.**
- **Send e-mail correspondence for PatentIn software program help to ebc@uspto.gov**
- **Patent software is available at http://www.uspto.gov/patents/resources/tools/checker/patentinrel.jsp .**

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **70** surcharge.
- $(**0**) previous unapplied payment amount.
- $ **70** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Gregory Porreca
  Uri Laserson

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/tle/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	NOT YET ASSIGNED
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

FILED ELECTRONICALLY

STATEMENT IN SUPPORT OF COMPUTER READABLE FORM SUBMISSION

I hereby state that the content of the paper copy and computer readable forms of the Sequence Listing, submitted in the above-identified application are the same. No new matter is added.

Dated: October 19, 2016

Respectfully submitted,
BROWN RUDNICK LLP

BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
Tel: (617) 856-8434
Fax: (617) 856-8201

/Thomas C. Meyers/
Thomas C. Meyers, Reg. No. 36,989
Attorney for Applicants
Email: tmeyers@brownrudnick.com

FIG. 1

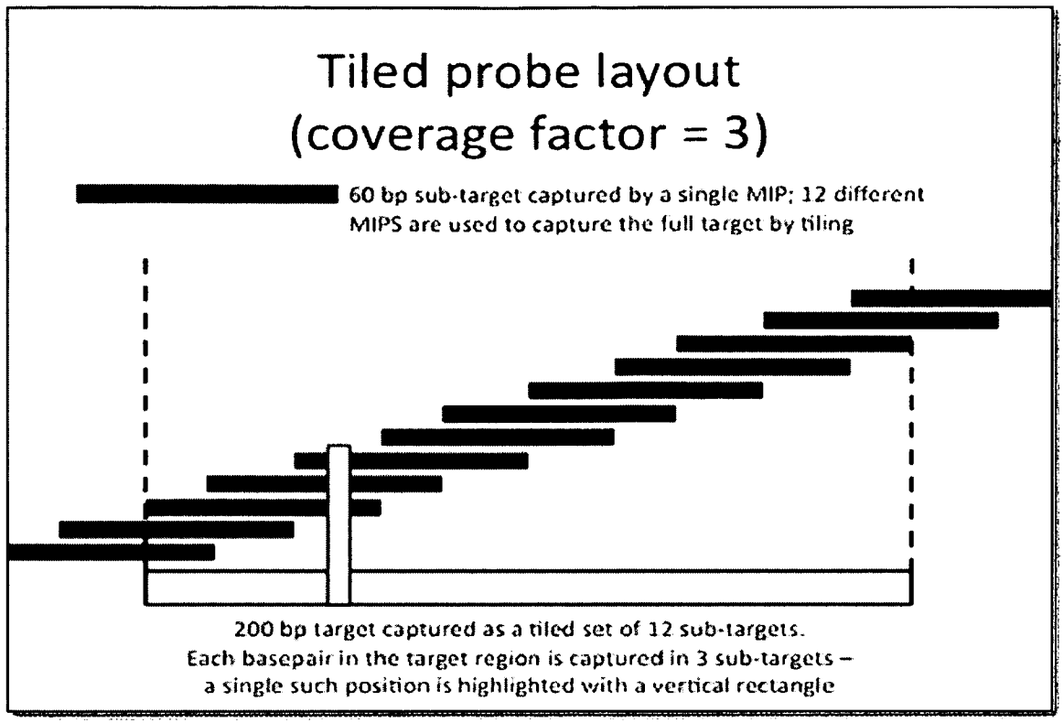

Tiled probe layout
(coverage factor = 3)
60 bp sub-target captured by a single MIP; 12 different MIPS are used to capture the full target by tiling
200 bp target captured as a tiled set of 12 sub-targets.
Each basepair in the target region is captured in 3 sub-targets –
a single such position is highlighted with a vertical rectangle

FIG. 2

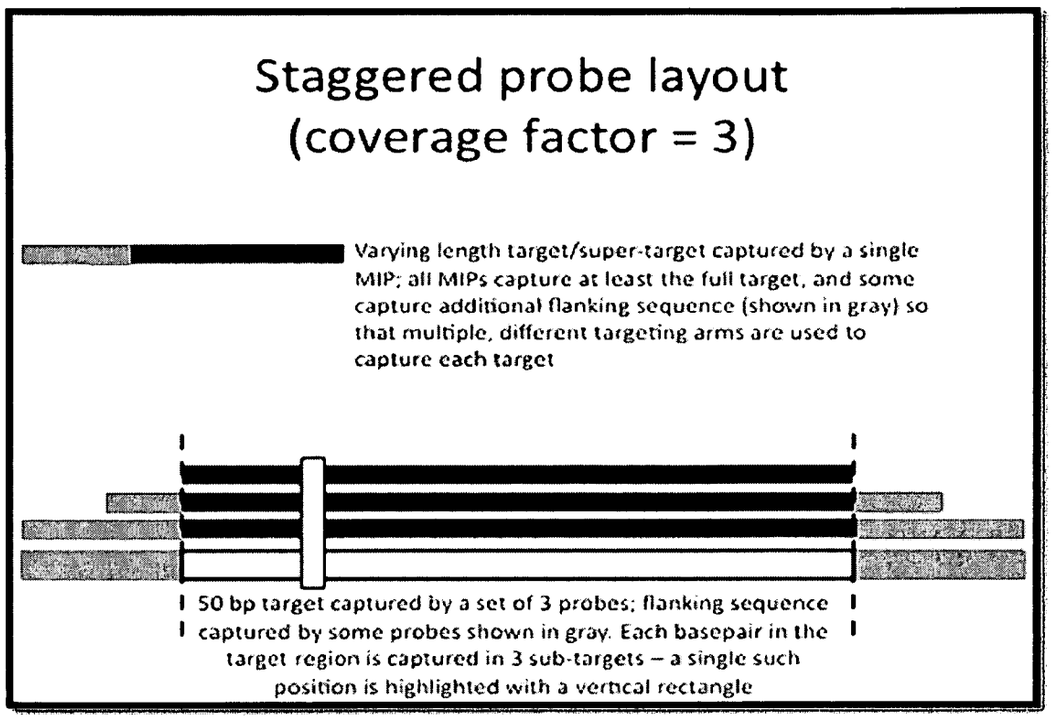

Staggered probe layout
(coverage factor = 3)
Varying length target/super-target captured by a single MIP; all MIPs capture at least the full target, and some capture additional flanking sequence (shown in gray) so that multiple, different targeting arms are used to capture each target
50 bp target captured by a set of 3 probes; flanking sequence captured by some probes shown in gray. Each basepair in the target region is captured in 3 sub-targets – a single such position is highlighted with a vertical rectangle

FIG. 3

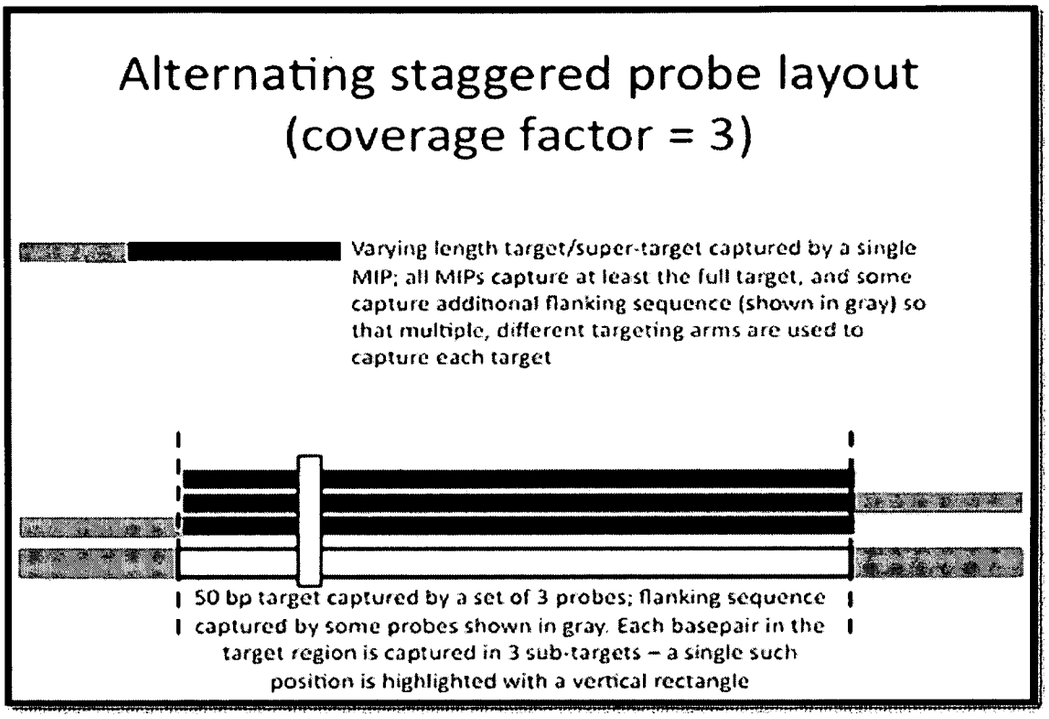

Alternating staggered probe layout
(coverage factor = 3)
Varying length target/super-target captured by a single MIP; all MIPs capture at least the full target, and some capture additional flanking sequence (shown in gray) so that multiple, different targeting arms are used to capture each target
50 bp target captured by a set of 3 probes; flanking sequence captured by some probes shown in gray. Each basepair in the target region is captured in 3 sub-targets – a single such position is highlighted with a vertical rectangle

FIG. 4A

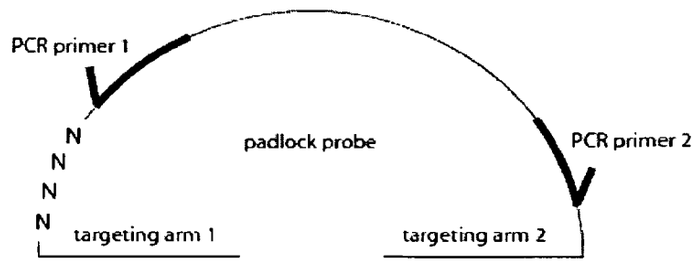


FIG. 4B

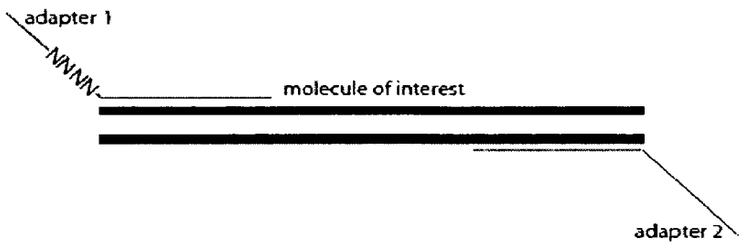


FIG. 4C

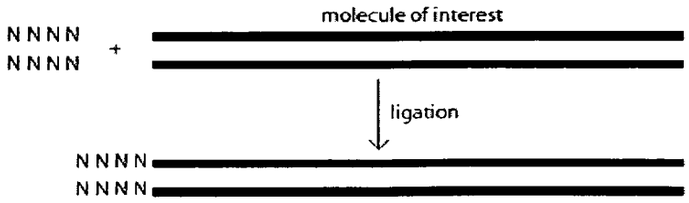


FIG. 5

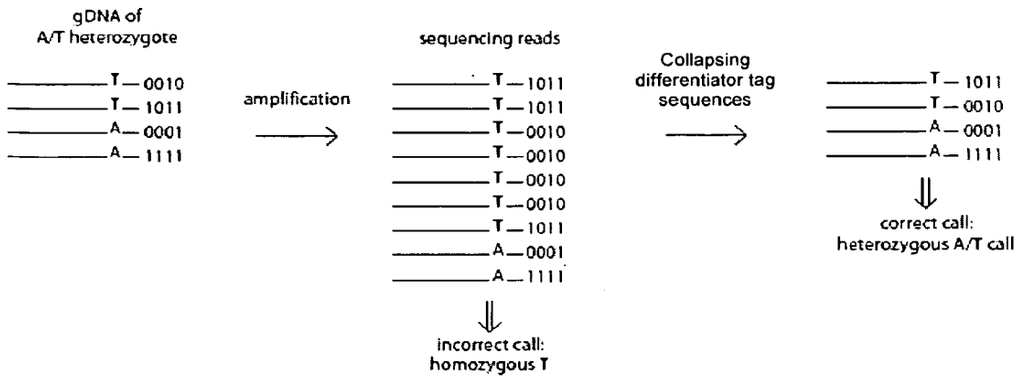

gDNA of
A/T heterozygote
T — 0010
T — 1011
A — 0001
A — 1111
amplification
sequencing reads
T — 1011
T — 1011
T — 0010
T — 0010
T — 0010
T — 0010
T — 1011
A — 0001
A — 1111
incorrect call:
homozygous T
Collapsing
differentiator tag
sequences
T — 1011
T — 0010
A — 0001
A — 1111
correct call:
heterozygous A/T call

FIG. 6

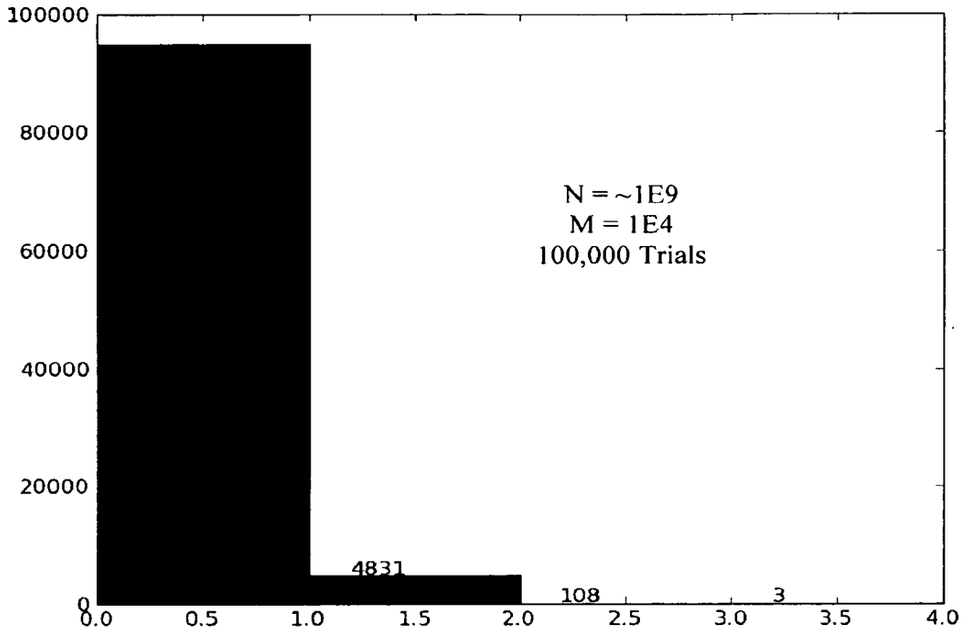

100000
80000
60000
40000
20000
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
N = ~1E9
M = 1E4
100,000 Trials
4831
108
3
Independent Occurrences of
Target:Differentiator Tag Sequence
100,000 Trials

FIG. 7

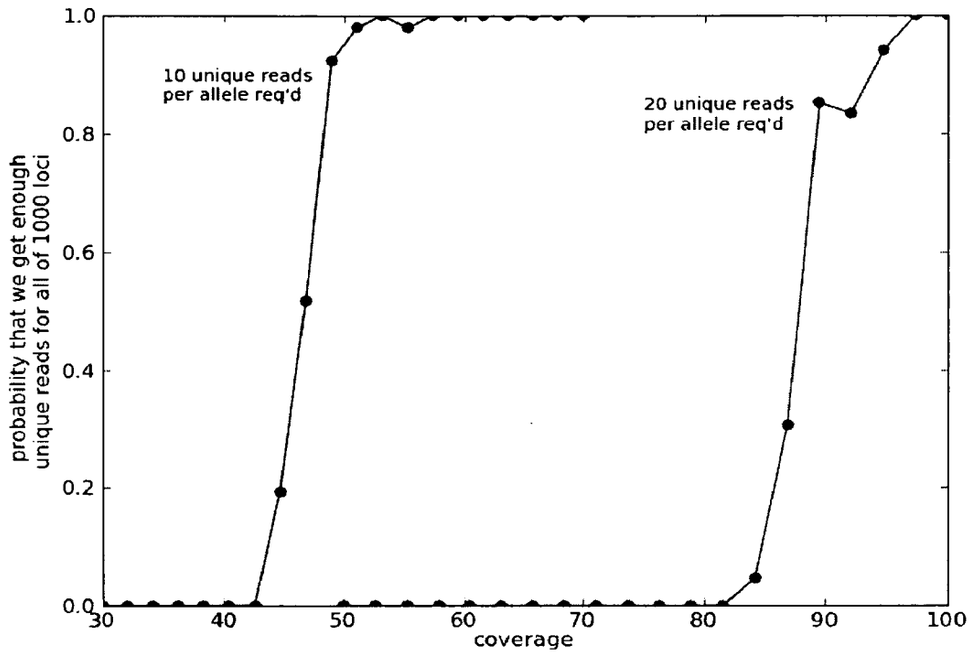

1.0
0.8
0.6
0.4
0.2
0.0
probability that we get enough unique reads for all of 1000 loci
10 unique reads per allele req'd
20 unique reads per allele req'd
30
40
50
60
70
80
90
100
coverage

FIG. 8

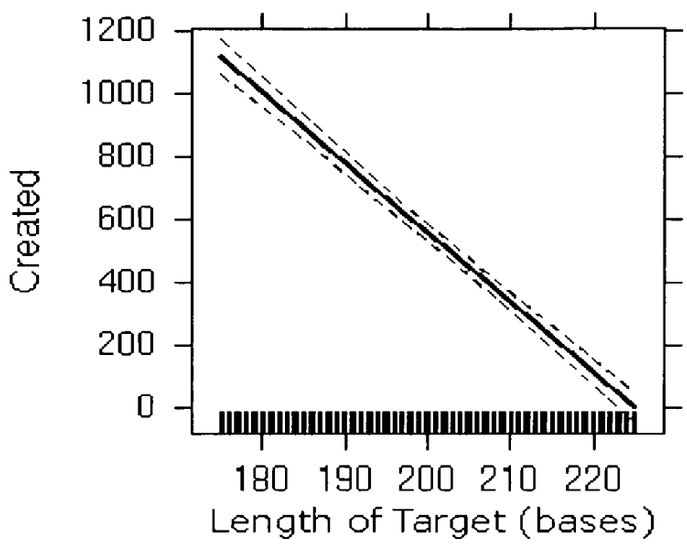

1200
1000
800
600
400
200
0
Created
180
190
200
210
220
Length of Target (bases)

FIG. 9

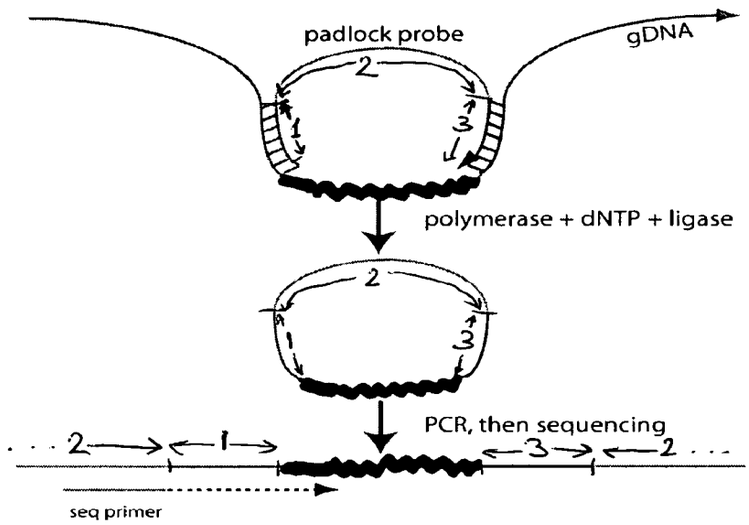

padlock probe
gDNA
2
1
3
polymerase + dNTP + ligase
2
1
3
PCR, then sequencing
. . . 2
1
3
2 . . .
seq primer

FIG. 10

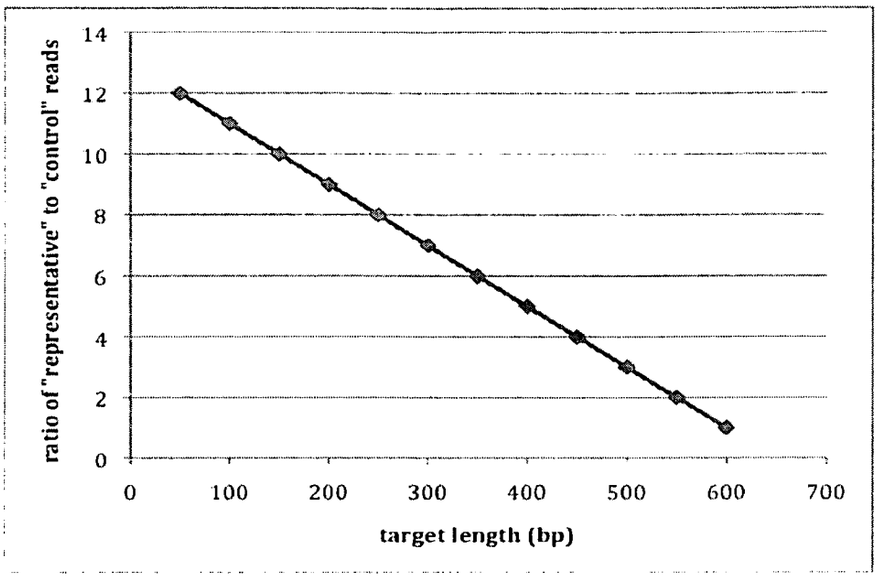

ratio of "representative" to "control" reads
14
12
10
8
6
4
2
0
0
100
200
300
400
500
600
700
target length (bp)

FIG. 11A

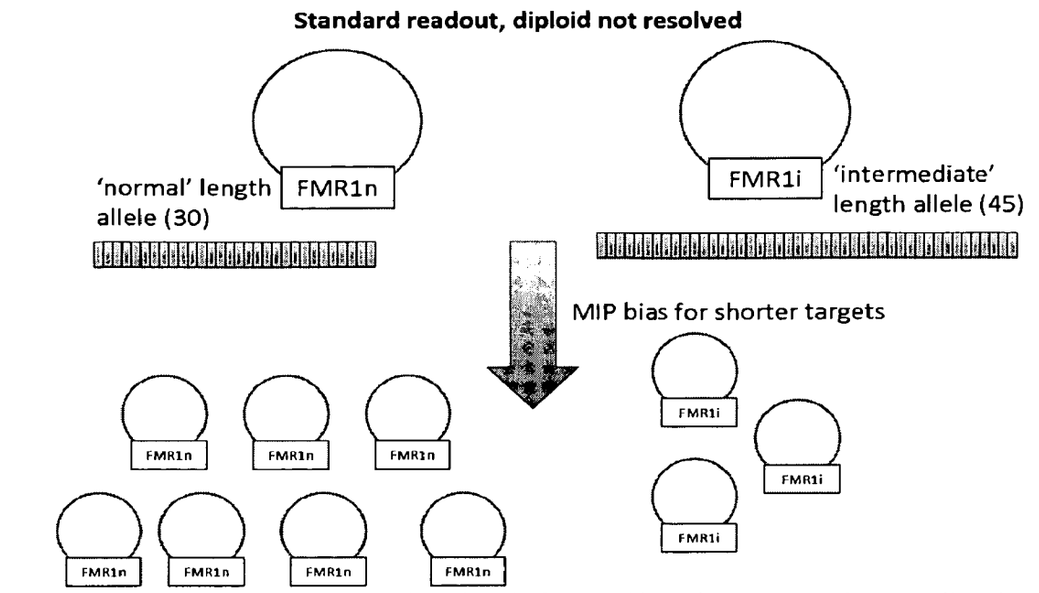

Standard readout, diploid not resolved
'normal' length allele (30)
FMR1n
FMR1i
'intermediate' length allele (45)
MIP bias for shorter targets
FMR1n
FMR1n
FMR1n
FMR1n
FMR1n
FMR1n
FMR1n
FMR1i
FMR1i
FMR1i
Readout: sum of alleles appears as 'long' end of normal length range, not intermediate het

FIG. 11B

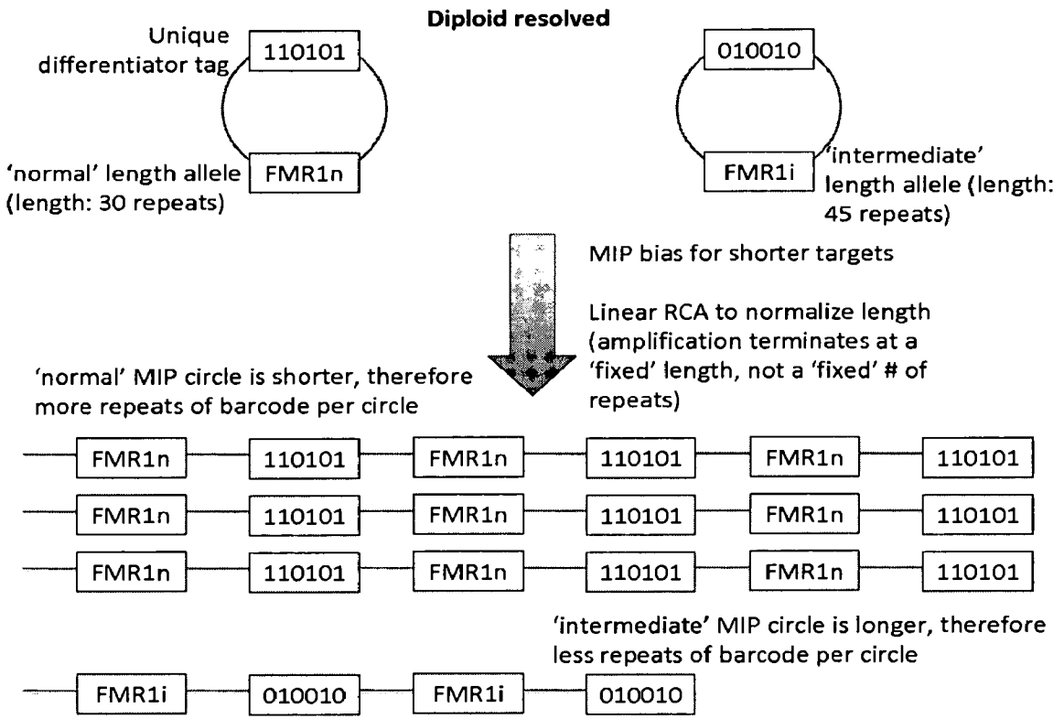

Diploid resolved
Unique differentiator tag
110101
'normal' length allele (length: 30 repeats)
FMR1n
010010
FMR1i
'intermediate' length allele (length: 45 repeats)
MIP bias for shorter targets
Linear RCA to normalize length (amplification terminates at a 'fixed' length, not a 'fixed' # of repeats)
'normal' MIP circle is shorter, therefore more repeats of barcode per circle
FMR1n
110101
'intermediate' MIP circle is longer, therefore less repeats of barcode per circle
FMR1i
010010

FIG. 11C

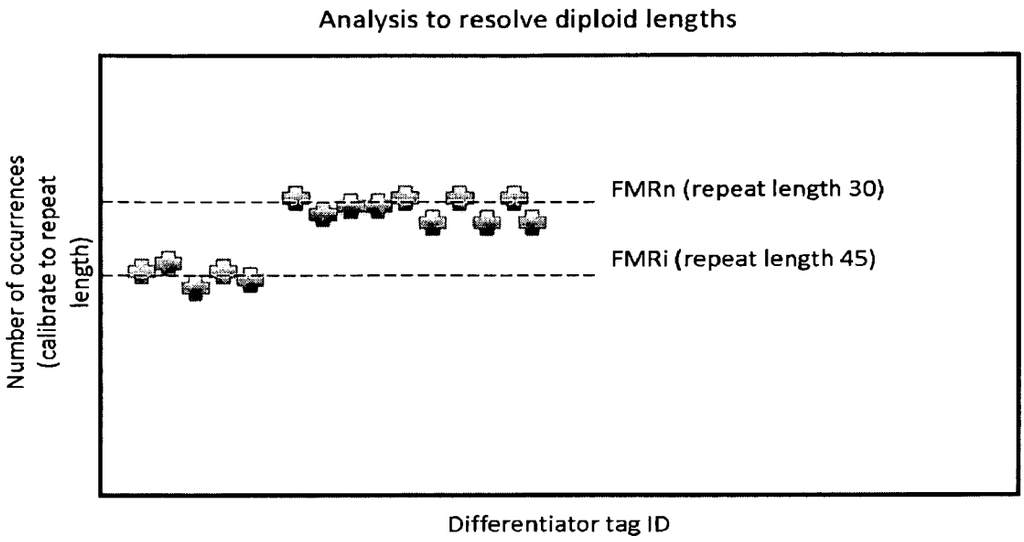

Analysis to resolve diploid lengths
Number of occurrences (calibrate to repeat length)
FMRn (repeat length 30)
FMRi (repeat length 45)
Differentiator tag ID

FIG. 12

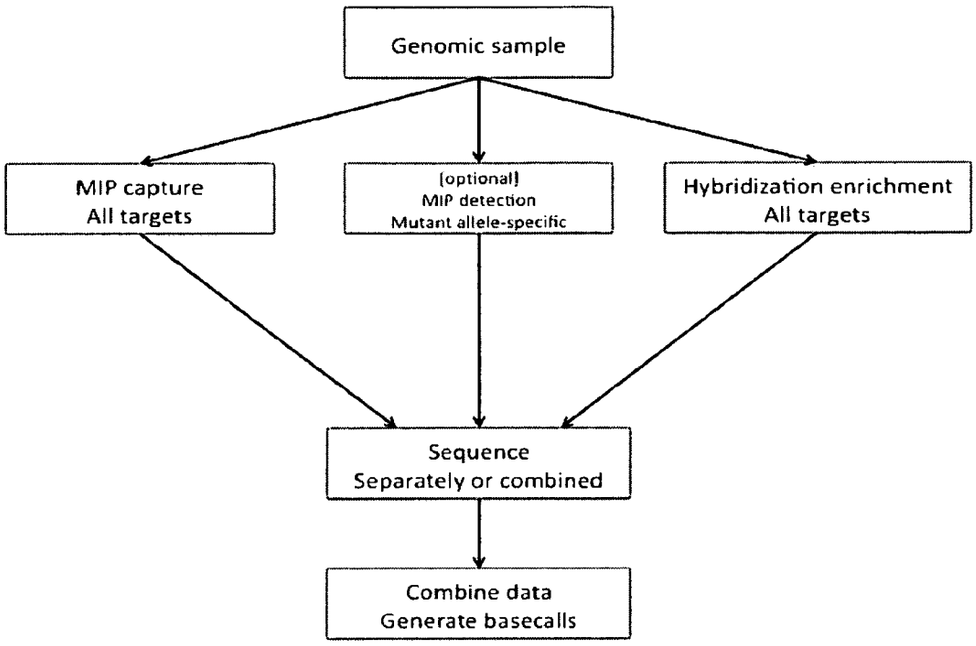

Genomic sample
MIP capture
All targets
(optional)
MIP detection
Mutant allele-specific
Hybridization enrichment
All targets
Sequence
Separately or combined
Combine data
Generate basecalls

FIG. 13

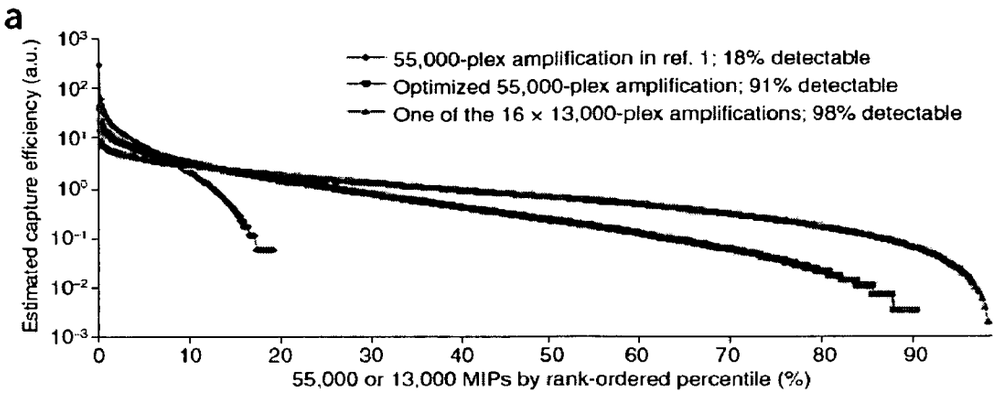
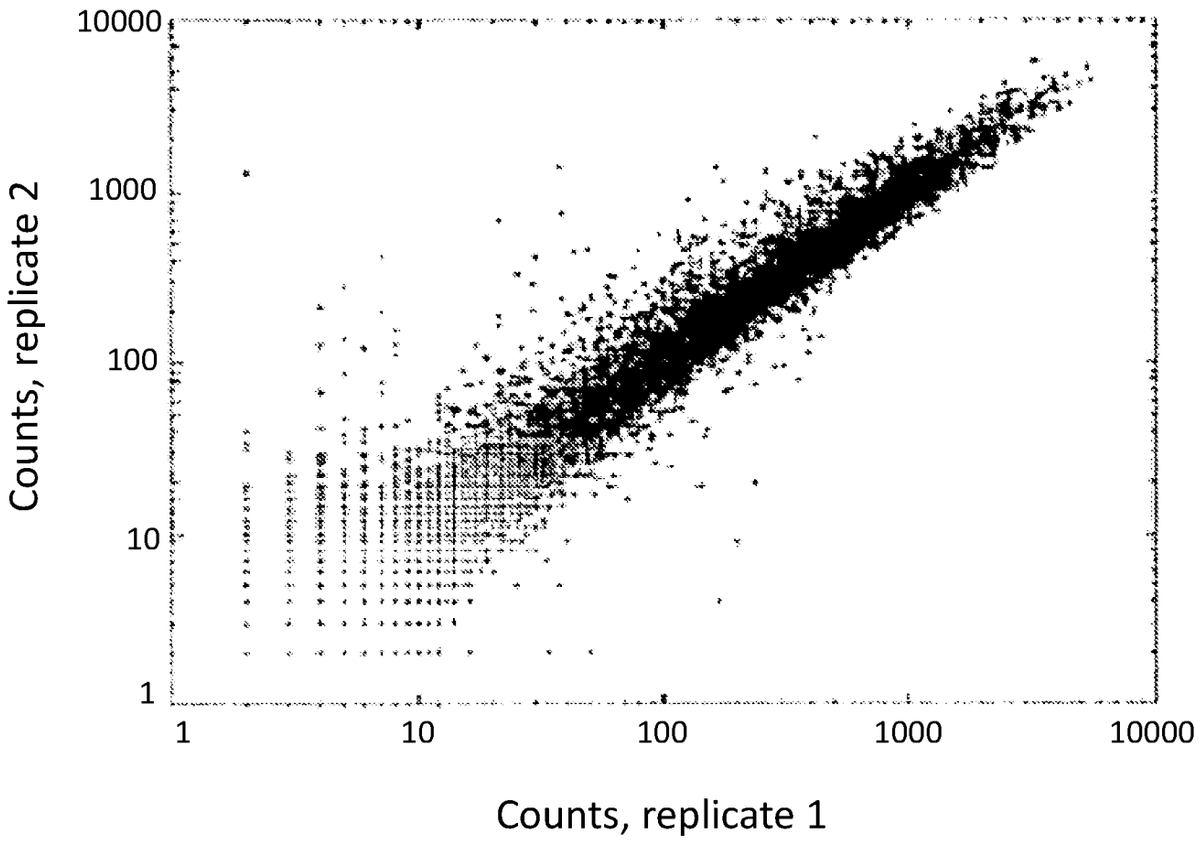

a
Estimated capture efficiency (a.u.)
10³
10²
10¹
10⁰
10⁻¹
10⁻²
10⁻³
0
10
20
30
40
50
60
70
80
90
55,000 or 13,000 MIPs by rank-ordered percentile (%)
55,000-plex amplification in ref. 1; 18% detectable
Optimized 55,000-plex amplification; 91% detectable
One of the 16 × 13,000-plex amplifications; 98% detectable

FIG. 14


10000
1000
100
10
1
Counts, replicate 2
1
10
100
1000
10000
Counts, replicate 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	NOT YET ASSIGNED
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

This paper is in response to the Notice to File Corrected Application Papers mailed from the United States Patent and Trademark Office on August 23, 2016.

Applicants pay the surcharge under 37 CFR 1.16(f). Applicants believe no other fee is due with this response. Nevertheless, if any fee is required, Applicants authorize such fee to be taken out of Deposit Account No. 50-0369.

Amendments to the specification begin on page 2.

Remarks begin on page 3.

Amendments to the specification

Please amend page 1 of the specification by inserting the following section after the RELATED APPLICATIONS section:

SEQUENCE LISTING

This application contains a sequence listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. The ASCII-formatted sequence listing, created on October 17, 2016, is named GSGE-002-04US-Sequence-Listing, and is 61,754 bytes in size.

Please amend page 27, lines 1-3, of the specification as follows:

~~FIGs. 4A, B, and C~~ FIGS. 4A-C depict various non-limiting methods for combining differentiator tag sequence and target sequences (NNNN depicts a differentiator tag sequence);

Petitioner Illumina, Inc., EX1003, p. 251

Remarks

Applicant hereby amends the specification and drawings. No new matter is added.

Drawings

Applicant amends the drawings under 37 CFR 1.121(d) by submitting sixteen (16) sheets of replacement drawings. The drawings are amended to comply with 37 CFR 1.84. In particular, the drawings are amended to correct the labeling of the several views, and FIG. 14 is corrected to be electronically reproducible. Additionally, the specification is amended to correspond to the relabeled drawings. No new matter is added.

Sequence Listing

Applicant hereby amends the specification to add a reference to the Sequence Listing. Applicant submits herewith a paper copy of the Sequence Listing, a copy of the Sequence Listing in computer readable form, an amendment specifically directing its entry into the application, and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written sequence listing and includes no new matter.

Conclusion

Applicants submit that by this response, the informalities have been corrected and the application is complete and ready to be docketed for examination, an action that is respectfully requested. If there are any questions or comments concerning this response, the Examiners are invited and encouraged to contact Applicants' undersigned representative.

Dated: October 21, 2016

Respectfully submitted,
BROWN RUDNICK LLP

/Thomas C. Meyers/

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FaxNumber :
EmailAddress :
<110> OrganizationName : Good Start Genetics, Inc.

Individual Applicant

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City :
State :
Country :
PostalCode :
PhoneNumber :
FaxNumber :
EmailAddress :
<110> LastName : Porreca
<110> FirstName : Gregory
<110> MiddleInitial :
<110> Suffix :

Individual Applicant

Street :
City :
State :
Country :
PostalCode :
PhoneNumber :
FaxNumber :
EmailAddress :
<110> LastName : Laserson
<110> FirstName : Uri
<110> MiddleInitial :
<110> Suffix :

Application Project

<120> Title : METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
<130> AppFileReference : GSGE-002/04US 29258/78
<140> CurrentAppNumber : 15/231,687
<141> CurrentFilingDate : 2016-08-08

Earlier Applications

<150> PriorAppNumber : 13/266,862
<151> PriorFilingDate : 2012-03-13

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tcacatcacc aagttaaaaa aaaaaarggg gcgggggggc agaatgaaaa tt 52
<212> Type : DNA
<211> Length : 52
SequenceName : 1
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaacaaggat gaattaagtt ttttttaaa aaagaaacat ttggtaaggg ga 52
<212> Type : DNA
<211> Length : 52
SequenceName : 2
SequenceDescription :

Feature

Sequence: 2:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atcaccaagt taaaaaaaaa aaagggrcgg gggggcagaa tgaaaattgc at 52
<212> Type : DNA
<211> Length : 52
SequenceName : 3
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctattgaacc agaaccaaac aggaatrcca tagcattttg taaactaaac tg 52
<212> Type : DNA
<211> Length : 52
SequenceName : 4
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
caggagttca agaccagcct actaaamcac acacacacac acacacacac ac 52
<212> Type : DNA
<211> Length : 52
SequenceName : 5
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gattaaataa tagtgtttat gtacccsgct tataggagaa gagggtgtgt gt 52
<212> Type : DNA
<211> Length : 52
SequenceName : 6
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens

<400> PreSequenceString :
attgttatct tttcatataa ggtaacwgag gcccagagag attaaataac at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 7
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taattttaat taagtaaatt taattgrtag ataaataagt agataaaaaa ta 52
<212> Type : DNA
<211> Length : 52
SequenceName : 8
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtataaaaaa aaaaaaaaaa aaagttwgaa tgttttcttg cattcagagc ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 9
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atactaaaaa tttaaagttc tcttgcrata tattttctta atatcttaca tc 52
<212> Type : DNA
<211> Length : 52
SequenceName : 10
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgctgggatt acaggcgtga gccaccrcgc ctggcctgat gggacatatt tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 11
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctacaatata agtatagtat tgcaaamcca tcaggaaggg tgttaactat tt 52
<212> Type : DNA
<211> Length : 52
SequenceName : 12
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens

<400> PreSequenceString :
gttgtctcca aacttttttt caggtgagaa ggtggccaac cgagcttcgg aaag 54
<212> Type : DNA
<211> Length : 54
SequenceName : 13
SequenceDescription :

Feature

Sequence: 13:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 29
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttttttcata aaagattata taaaggmtat tgcttttgaa tcacaaacac ta 52
<212> Type : DNA
<211> Length : 52
SequenceName : 14
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atctagtgag cagtcaggaa agagaayttc cagatcctgg aaatcagggt ta 52
<212> Type : DNA
<211> Length : 52
SequenceName : 15
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tagagtataa aaaaaaaaaa aaaaaaagtt tgaatgtttt cttgcattca ga 52
<212> Type : DNA
<211> Length : 52
SequenceName : 16
SequenceDescription :

Feature

Sequence: 16:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgcaaatgcc aactatcaaa gatattsgag tatactgtca ataaacttca ta 52

<212> Type : DNA
<211> Length : 52

SequenceName : 17
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tcctcaacag ttagaaacaa tattttsagt gaittcccat gccaacttta ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 18
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttttggtat tgttgttaaa taagtgrgaa ttcaatacag tataatgtct gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 19
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cttgaaatcg gatatatata tatatatgta tatatatata tatatatata tatatataca 60
tatatatata tagtattatc cctgttttca cagtttt 97
<212> Type : DNA
<211> Length : 97
SequenceName : 20
SequenceDescription :

Feature

Sequence: 20:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 72
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agaggggctg tgaaggacac caaggargag actaagagcc aggagggaaa ac 52

<212> Type : DNA
<211> Length : 52
SequenceName : 21
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tagagtttat tagcttttac tactctrctt agttactttg tgttacagaa ta 52

<212> Type : DNA

<211> Length : 52
SequenceName : 22
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
actagtgatg atgagcttct tttcatatgt ttgttggctg cataaatgtc ttc 53

<212> Type : DNA
<211> Length : 53
SequenceName : 23
SequenceDescription :

Feature

Sequence: 23:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gcagagaaaa gaggggctgt gaaggasacc aaggaggaga ctaagagcca gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 24
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttcagaggtc taccactggt gcatackcta atcacagtgt cgaaaatttt ac 52

<212> Type : DNA
<211> Length : 52
SequenceName : 25
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aagaaagagc aaaagagggc aaacttytca tacatttttg atgtcgaaac ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 26
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cctaaagttt aaaaagaaaa aaaaaaagga agaaggaatt aaaaatccaa ag 52

<212> Type : DNA
<211> Length : 52
SequenceName : 27
SequenceDescription :

Feature

Sequence: 27:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtgtgtgtgt gtatatatat atatatwtat atatttttt tttcctgagc ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 28
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaactgttga tgttttcatt tatttasatc attggaaaac tttagattct ag 52
<212> Type : DNA
<211> Length : 52
SequenceName : 29
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttatccatt cttaaccaga acagacrttt tttcagagct ggtccaggaa aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 30
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttgaaatcgg atatatatat atatatrtat atatatatat atatatatat at 52
<212> Type : DNA
<211> Length : 52
SequenceName : 31
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tagtttttta tttcctcata ttattttcag tggctttttc ttccacatct tt 52
<212> Type : DNA
<211> Length : 52

SequenceName : 32
SequenceDescription :

Feature

Sequence: 32:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
acatagttct cagtggtaca actacargtg atttctcttt tcttatttct gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 33
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agagcaatgg catcccttgt cttgtgytat acaggatgca gcaatttata gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 34
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttctgtctac ataagatgtc atactaratt atcttttcca gcatgcattc ag 52

<212> Type : DNA
<211> Length : 52
SequenceName : 35
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cagggtggca tgttaggcag tgcttaraat aaatgagttg gttatacaag ta 52

<212> Type : DNA
<211> Length : 52
SequenceName : 36
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aggacacaca cacacacaca cacacacatg cacacacatt taaatagatg cat 53
<212> Type : DNA
<211> Length : 53

SequenceName : 37
SequenceDescription :

Feature

Sequence: 37:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Feature

Sequence: 37:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taaaaaattg gtataatgaa attgcayttg tagtctttgg acatttaaat cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 38
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttcaatact taagaggtac gcagagraaa gaggggctgt gaaggacacc aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 39
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cagcaatgaa tattttgagg ctgaggygct gaggggtaaa attgcagcct gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 40
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttatggttta tatttttgtg tcttctcttt aacacatctt ttctagcaga attca 55

<212> Type : DNA
<211> Length : 55
SequenceName : 41

SequenceDescription :

Feature

Sequence: 41:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 30
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtattttagt ttttttttt tgtttgtttt gttttgtttt gttttgtttt tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 42
SequenceDescription :

Feature

Sequence: 42:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgggtgactc catttttact tttagtytgg tctgttgagg cctcgtgaga ga 52

<212> Type : DNA
<211> Length : 52
SequenceName : 43
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tattttcatg tattttagtt ttttttttt gtttgttttg ttttgttttg ttttg 55

<212> Type : DNA
<211> Length : 55
SequenceName : 44
SequenceDescription :

Feature

Sequence: 44:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 30
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtgtgtgtgt atatatatat atatatwtat attttttttt tcctgagcca aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 45
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aacctattag catgtctggc agaaaaatag atacttaata aatttcttaa at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 46
SequenceDescription :

Feature

Sequence: 46:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gaggcttaga cagtttaagt aactcargca tggttacaca actagctagg gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 47
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtgtgagtat tatgagacca tatgttrgga gattttattt ggtattgagg at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 48
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gaaaccccac cccttctata gttttcyctt taatatttac aatggaacca tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 49
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
catatatata tagtgtgtgt gtgtgtrtat atatatatat atatatattt tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 50
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cgagcgagag agagagagag agagagagga gccggcgcga gaactacgca tgc 53

<212> Type : DNA
<211> Length : 53
SequenceName : 51
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ggcaggtaat atctagtacc ttacttwtat ttcctgagca cattctacat tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 52
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ggccaggaat gggagtgctt aggtgcrgag gtggcactgt tcccgcagct gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 53
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgaaaactcc atcccctcag ggtcatyaga tgaagagaag accacagggg tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 54
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgtaggtaag ggtcacatgt gggagasgca gctgtgggta ggtcagccct gt 52

<212> Type : DNA
<211> Length : 52

SequenceName : 55
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccaagaaggc gccattacac tccagcctgg gcgacagggc gagactccct ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 56
SequenceDescription :

Feature

Sequence: 56:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgccacaccc agctaatttg tgtgtggtat gtgtgtgtat gtatgtgtgt gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 57
SequenceDescription :

Feature

Sequence: 57:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gttcctccag taatttttt ttttttggt tttgagacag agtcttgccc tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 58
SequenceDescription :

Feature

Sequence: 58:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atcatgccca gataattttt tttttttgta ttttagtaga cacagggttt ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 59
SequenceDescription :

Feature

Sequence: 59:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cgagcgagag agagagagag agagagagga gccggcgcga gaactacgca tgc 53

<212> Type : DNA
<211> Length : 53
SequenceName : 60
SequenceDescription :

Feature

Sequence: 60:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cctgtgaggg gcacattcct tagtagctaa ggagttgggg gtgtgaagat cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 61
SequenceDescription :

Feature

Sequence: 61:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens

Petitioner Illumina, Inc., EX1003, p. 266

<400> PreSequenceString :
acaggctact ggctgggccc aggcaaaggg ggccttggca ggaaaagttc ct 52
<212> Type : DNA
<211> Length : 52
SequenceName : 62
SequenceDescription :

Feature

Sequence: 62:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gcgagagaga gagagagaga gagaggagag ccggcgcgag aactacgcat gcg 53
<212> Type : DNA
<211> Length : 53
SequenceName : 63
SequenceDescription :

Feature

Sequence: 63:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aagaagaaaa ataaaaagaa agtgggycag accgagagaa caggaagcct ga 52
<212> Type : DNA
<211> Length : 52
SequenceName : 64
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaggacaaag gcaaagagac aaaggckcaa cactgggggt ccccagagag tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 65
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tacctagtca cttcctgcct ccatggygca aaaggggatg ggtgtgcctc tt 52

<212> Type : DNA

<211> Length : 52
SequenceName : 66
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctcttccgag gttccaccct gaacacyttc ctgctccctc gtggtgtaga gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 67
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttctgactgg caaccagccc cactctytgg gagccctcag gaatgaactt gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 68
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gctcagcctc ccaggctgga gtgcagwggc gcgatctcgg ctcaccgcaa cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 69
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
catgaaccac atcaaatgag atttagyggg agtggcacac acagtcatga cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 70
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aagcagccct ggggagtcgg ggcgggrcct ggattggaaa agagacggtc ac 52

<212> Type : DNA
<211> Length : 52
SequenceName : 71
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :

ctccaagttc tgggagcaga gtgtgcrgct aggctcctgg gatcgaggga tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 72
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gttcctccag taatttttt ttttttkgtt ttgagacaga gtcttgccct gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 73
SequenceDescription :

Feature

Sequence: 73:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctagtacctt acttccctca agttcawtca tctcacagat atttcctgag ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 74
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aattagccgt gcgtggtggc gggtgcytgt aatcccacgt acttgggagg ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 75
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccatggccag ccggggaggg gacgggmaca cacagaccca cacagagact ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 76
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens

<400> PreSequenceString :
agcgagagag agagagagag agagagrgag ccggcgcgag aactacgcat gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 77
SequenceDescription :

Feature

Sequence: 77:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cgtagcagtt agcagatgat aggcggbgaa atcttatttc acagggcatt aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 78
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctggccctgg tgacagtggg gctgtgygtg gggccagagc cttctcagag gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 79
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cagatactgg ccctggtgac agtgggrctg tgcgtggggc cagagccttc tc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 80
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gacagatact ggccctggtg acagtgkggc tgtgcgtggg gccagagcct tc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 81
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ggctcctctc tctctctctc tctctctcgc tcgctctctc gctctctcgc tct 53

<212> Type : DNA
<211> Length : 53
SequenceName : 82
SequenceDescription :

Feature

Sequence: 82:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtttcagacc agcctggcca acatagygaa accccatctc tactaaaaat aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 83
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agtgggcgat tggatggagc tgagtayggg gcccatccag gctaatcaca cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 84
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccgggctccg tgaatgtttg tcacatstct gaagaacgta tgaattacat aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 85
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gaatcccaac cccgacgctc gtcgccsggc tccgtgaatg tttgtcacat gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 86
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gcgaatccca accccgacgc tcgtcgycgg gctccgtgaa tgtttgtcac at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 87
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgggcagaag tcagggtcca aagaaakggc aaagaaaagt gtcagtggct ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 88
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taagaaagac gtttttgatt ttttтcrgac ttctctggct ccactaccct gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 89
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctgattcctg gccaggagcg gtggctyacg cctgtaatcc cagcgctttg gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 90
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taaaaatgct gattcctggc caggagyggt ggctcacgcc tgtaatccca gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 91
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttaaaaatg ctgattcctg gccaggmgcg gtggctcacg cctgtaatcc ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 92

SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
caagacctgt caaagatctg agaaatwtta cccgacttac aagctaacca tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 93
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
actgtaataa gtgctgtaaa agaaatrcac aaaataatat agcagagggt at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 94
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cttgaggtca ggagttcaag accagtytgg gcaacatggg gaaaaccttg tc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 95
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aggttgcagt gagccgagat catgccrttg cactccagcc ggggcaacaa aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 96
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
acaagtgtct tgaaattatc tgtgatytgc tatagagcaa tacttttgta aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 97
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtgggtatat gcagctctat gcactayctg ctcatttatt tggtaaatct aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 98
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgtgtgtgtg tgcgtgtgtg tgtgtgtgtg tgtgatcata agagtggctg cagcaaact 59

<212> Type : DNA
<211> Length : 59
SequenceName : 99
SequenceDescription :

Feature

Sequence: 99:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 34
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agtctggagt gcaatggtgc aatctcrgct cactgcagcc tccacctccg gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 100
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctcctaatgg atatttccta aattttkctg aacagaattt aacttgagct gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 101
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atttaaaaat ggatttctag aaaaacratc acatacttga atattttagc aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 102
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctataaatgg gtagcatgag ggattcragg aggtggctga aagaagcacg ta 52

<212> Type : DNA
<211> Length : 52
SequenceName : 103
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aagaaaccaa gcatagtaga gtgttaraaa accaaagcaa ctaaacaact gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 104
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cggggctcag aacttgtaac agaaaawtaa aatatactcc actcaaggga at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 105
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tactacactt cacggatact gtacttgtac ttttttcca aattgaaggt ttttggc 57

<212> Type : DNA
<211> Length : 57
SequenceName : 106
SequenceDescription :

Feature

Sequence: 106:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 32
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttgtttttgt ttttgttttt gtttttgttt ttgtttttg agatggagtc tcgctctgtc 60
gcc 63
<212> Type : DNA
<211> Length : 63
SequenceName : 107
SequenceDescription :

Feature

Sequence: 107:
<221> FeatureKey : misc_feature

<222> LocationFrom : 27
<222> LocationTo : 38
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttgccttac tacacttcac ggatactgta cttgtacttt ttttccaaat tgaaggt 57

<212> Type : DNA
<211> Length : 57
SequenceName : 108
SequenceDescription :

Feature

Sequence: 108:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 32
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gaggtggctg aaagaagcac gtatccctga tggcatggtt gcgggttata tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 109
SequenceDescription :

Feature

Sequence: 109:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gagaaaagca gttcctggaa cacccccacc ccttaacccc ttatctctgc tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 110
SequenceDescription :

Feature

Sequence: 110:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present

CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttacatatgt atacatgtgc catgtttggt gtgccgcacc cattaactcg tc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 111
SequenceDescription :

Feature

Sequence: 111:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctttttccag attttttttt ttttttgag acagagtttc actcttgttg cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 112
SequenceDescription :

Feature

Sequence: 112:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttggaaatc ttaagctttt atttgggtgt cacagagaaa caggatctgt at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 113
SequenceDescription :

Feature

Sequence: 113:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tactttaagt tttagggtac atgtgcacca tgtgcaggtt tgttacatat gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 114
SequenceDescription :

Feature

Sequence: 114:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
attcatgacc agccacataa atgcacagta ttacttcgca agcatgccaa tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 115
SequenceDescription :

Feature

Sequence: 115:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtgcactaga attagctaaa gtgggggaaa aaaagatgca tttgatggtc ta 52

<212> Type : DNA
<211> Length : 52
SequenceName : 116
SequenceDescription :

Feature

Sequence: 116:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :

aacctccacc tcccaggttc aagagaattc tcctgcctca gcctcccaag ta 52

<212> Type : DNA
<211> Length : 52
SequenceName : 117
SequenceDescription :

Feature

Sequence: 117:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cctccctgtg atccgaagta gcagacrtac ttaacttcca tggtggattg tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 118
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaaacattat tatatctaga aaaaaaatgt atcttaacca ttgtgggaag tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 119
SequenceDescription :

Feature

Sequence: 119:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttgaaggtaa aatcataggg agttgggagc tgtcctcttg cgctgaatca gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 120
SequenceDescription :

Feature

Sequence: 120:
<221> FeatureKey : modified_base
<222> LocationFrom : 27

<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
acttgtggcc tttttggaga ggttagcaac tctgaaaact ctgtccctgg acc 53

<212> Type : DNA
<211> Length : 53
SequenceName : 121
SequenceDescription :

Feature

Sequence: 121:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gaaggagaaa aagagaggaa ataagttaaa ataataaaca caattaataa ag 52

<212> Type : DNA
<211> Length : 52
SequenceName : 122
SequenceDescription :

Feature

Sequence: 122:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
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tgtatacatg tgccatgttg gtgtgcygca cccattaact cgtcatttag ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 123
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tcacctgtca cctcctatag aactttcccc tgaccctcct ctatagcatt aa 52

<212> Type : DNA
<211> Length : 52

SequenceName : 124
SequenceDescription :

Feature

Sequence: 124:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ataaatgatc atcattcaca gtaggggttt tgttttgttt tttttctgga aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 125
SequenceDescription :

Feature

Sequence: 125:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
acagacatat ctacaaacac acttttttcac atatttgtgt aagtcattta tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 126
SequenceDescription :

Feature

Sequence: 126:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaagacaact aaactaacgc tcaatgmaaa aagtattcgc tgctgtttac at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 127
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taccgtgtac cccgtgtttg tgaatgmggc cgcatattac gaaaagaaag aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 128
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cagggctgga ggtaaaacca tttattrcta accccagagc agtgaagaag tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 129
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttcttcattg cctattgaag agagagygga atgctttggt tgccagatat gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 130
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cacaagatct cattactcag gagctgycca agtgtctaat gtacttagtt aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 131
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttctgtgtaa catttcattt aagcaargga ttcggcaaat caaaaattgt ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 132
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taaaacgtat tgaaggtatt attgackctg ttgaagcaaa gagaacaaaa ca 52

<212> Type : DNA
<211> Length : 52

SequenceName : 133
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atctgctctt ccagttggat gacaagyctt gctgtctaac acctgctgca ga 52

<212> Type : DNA
<211> Length : 52
SequenceName : 134
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccatttttg ttgtattttt tttttcytga atacttttta tcgcagttgg tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 135
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccctgtctct aaaagaaaaa aaaaaaraaa aaaaaaagaa aacaaaaccc aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 136
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agtggctcca aaaaggtcat ggaaccyctt gaggatgatg caaattgact ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 137
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taaagttact tttcttttat tgactttccc ttatttttta accttatgct tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 138
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cagagttaaa aaaaaaaaaa aaaaaaagga agtagcagca acagcttgga aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 139
SequenceDescription :

Feature

Sequence: 139:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gttgcccagg gttgagtgca gaggcayatc ttggctcaca gcaacctctg cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 140
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaggcttttt ttttttttt ttttttttt gagacagagt cttgctgtgt caccc 55

<212> Type : DNA
<211> Length : 55
SequenceName : 141
SequenceDescription :

Feature

Sequence: 141:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 30
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
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gcctacattc tgcaaagagg agggaasatt cacagctcca tacttgaacc ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 142
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccaaaggaga atagctctag gggaggsagg tggatgagta tgcatggggg ag 52
<212> Type : DNA

<211> Length : 52
SequenceName : 143
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gactccatct caaaaaaaaa aaaaaaatgc agtctaatgg cagaattaga ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 144
SequenceDescription :

Feature

Sequence: 144:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttatttattt atttatttat ttttgaraca gggtctctgt tgtccaggct gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 145
SequenceDescription :

Sequence

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ttttgaggca gggtctcact ctgttgycca gggttgagtg cagaggcaca tc 52
<212> Type : DNA
<211> Length : 52
SequenceName : 146
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cgccttgcga aggccccaca gcttgcytgt gacaaacgtt cataggcaaa tg 52
<212> Type : DNA
<211> Length : 52
SequenceName : 147
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ggaggtctgt acaaagcacc acctacytca tgggtcagtt tccacagcag aa 52

<212> Type : DNA
<211> Length : 52

SequenceName : 148
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gaatcttata attcactgtg tacctccctc tgtttcatat tttcgcaatt gaact 55

<212> Type : DNA
<211> Length : 55
SequenceName : 149
SequenceDescription :

Feature

Sequence: 149:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 30
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aacatagtat ctaatatagc tttacaycca aagccaaaat atgaatacac tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 150
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttgttttgtt ttgtttgggg gggggggttg tttttctgag agggagtctt gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 151
SequenceDescription :

Feature

Sequence: 151:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
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cataccaaag ggcagctgga gggatayaga cggaagtcat gtggagagtg aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 152

SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
caggtgtgag ccaccacgac caccaawtta gctctttta ctccttccct tc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 153
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agtggtagct gattttgctt ctggatmctt tgccaccttc ccactcttta at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 154
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaagacctgt ttcttaaaaa aaaaaaagaa aaaaaaaaag aaagaaaaga aaagaaaaaa 60
acag 64
<212> Type : DNA
<211> Length : 64
SequenceName : 155
SequenceDescription :

Feature

Sequence: 155:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 39
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taaaaaatct ttcaatgagg agatgtyccc agagcaagac agctgtagga tg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 156
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaaagaaaaa aaaaaaaaaa aaaaaaagaa aacaaaaccc aaacccataa ag 52

<212> Type : DNA
<211> Length : 52

SequenceName : 157
SequenceDescription :

Feature

Sequence: 157:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cctgtctcta aaagaaaaaa aaaaaaraaa aaaaaagaaa acaaaaccca aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 158
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gttatcatag aaaaatatca cactctgtct gtatccccac ttccagaaac tgt 53

<212> Type : DNA
<211> Length : 53
SequenceName : 159
SequenceDescription :

Feature

Sequence: 159:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
caggagctca tagaattaca tacaatcttt ttttttttt tttgagacag cg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 160
SequenceDescription :

Feature

Sequence: 160:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttgagaatct tataattcac tgtgtacctc cctctgtttc atattttcgc aattg 55

<212> Type : DNA
<211> Length : 55
SequenceName : 161
SequenceDescription :

Feature

Sequence: 161:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 30
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
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ccactaccac agtgcctaga gaacaayatg tgtttaataa tatttaaata at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 162
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccctgtctct aaaagaaaaa aaaaaaaaaa aaaaaaagaa aacaaaaccc aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 163
SequenceDescription :

Feature

Sequence: 163:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccattatatc attcatttcc cactcatttt cttcattcca accaagatat at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 164
SequenceDescription :

Feature

Sequence: 164:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tccgtctcaa aaaaaaaaaa aaaaagagaa aggaattatt ctcatgtata ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 165
SequenceDescription :

Feature

Sequence: 165:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
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ctggggcagt taaaaagaaa aacaaacccc tggtccctgc ccttgaggag at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 166
SequenceDescription :

Feature

Sequence: 166:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctccagggtc ccattccagg accacacgcc tgctacctct gcagctcact ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 167
SequenceDescription :

Feature

Sequence: 167:
<221> FeatureKey : modified_base

<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ggattgacat ataccagtta gacggatttt ttttttccat aaaccaggct ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 168
SequenceDescription :

Feature

Sequence: 168:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
acaaataatt actacatatc tacaacrttc cagatacaga agaaatggcc aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 169
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taaacacact tgaaacatca tataaaatga tattactaca agacttaacc gtaa 54

<212> Type : DNA
<211> Length : 54
SequenceName : 170
SequenceDescription :

Feature

Sequence: 170:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 29
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
acacaggtaa tccatgttta ttatagaaaa atgccacatt actctttatt ga 52

<212> Type : DNA

<211> Length : 52
SequenceName : 171
SequenceDescription :

Feature

Sequence: 171:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agttatcata gaaaaatatc acactctgtc tgtatcccca cttccagaaa ctg 53

<212> Type : DNA
<211> Length : 53
SequenceName : 172
SequenceDescription :

Feature

Sequence: 172:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
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aatgaactta caggaaggta atatatggga aataaacatc ttattgaatt ta 52
<212> Type : DNA
<211> Length : 52
SequenceName : 173
SequenceDescription :

Feature

Sequence: 173:
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<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ggacccctga aaggcacaag acaccctttc aggttcacac ttcctgaaag ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 174
SequenceDescription :

Feature

Sequence: 174:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccaccaatca ccagagcctt ctgctcrggg gtacctgagg gaaaacaagc aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 175
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaagactgaa aaaacattca taactatttt tcttgttatc ctcggaaatg tc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 176
SequenceDescription :

Feature

Sequence: 176:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tatcttcatc ttggaggaga tgaggtygat ttcacctgct ggaagtccaa cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 177
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttgcctatga acgtttgtca cacttcygct gtgagttgct gaggcgaggt gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 178
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gcttgctgtt ggatacatct cgccatyacc tgccactctc tagcatcctg ga 52

<212> Type : DNA
<211> Length : 52
SequenceName : 179
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccggggcttg ctgttggata catctckcca ttacctgcca ctctctagca tc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 180
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctccgtttcg gtttcacttc 20
<212> Type : DNA
<211> Length : 20
SequenceName : 181
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atcttctctt cagccctgct 20
<212> Type : DNA
<211> Length : 20
SequenceName : 182
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gcacgatccg acggtagtgt 20
<212> Type : DNA
<211> Length : 20
SequenceName : 183
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ccgtaatcgg gaagctgaag 20
<212> Type : DNA
<211> Length : 20
SequenceName : 184
SequenceDescription :

Electronic Patent Application Fee Transmittal

Application Number:	15231687
Filing Date:	08-Aug-2016
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	2051	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**70**

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 15231687 Document Date: 10/21/2016

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

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- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

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============================================================
Sequence Listing could not be accepted due to errors.
See attached Validation Report.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Anjum, Durreshwar (CGI Federal)
Timestamp: [year=2016; month=10; day=31; hr=8; min=39; sec=45; ms=234; ]
============================================================


**********************************************************
Reviewer Comments:
1.


E248            Order Sequence Error <110> -> <110>; Expected Mandatory
Tag: <120> in Header
E248            Order Sequence Error <110> -> <110>; Expected Mandatory
Tag: <120> in Header
E248            Order Sequence Error <110> -> <110>; Expected Mandatory
Tag: <120> in Header
E248            Order Sequence Error <110> -> <110>; Expected Mandatory
Tag: <120> in Header
E248            Order Sequence Error <110> -> <110>; Expected Mandatory
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Tag: <120> in Header
E248            Order Sequence Error <110> -> <110>; Expected Mandatory
Tag: <120> in Header
E287            Invalid WIPO ST.2 date format; Use (YYYY-MM-DD) in <141>
E287            Invalid WIPO ST.2 date format; Use (YYYY-MM-DD)in <151>
E248            Order Sequence Error <151> -> <213>; Expected Mandatory
Tag: <210> in Header
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 59 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E248            Order Sequence Error <212> -> <211>; Expected Mandatory
Tag: <213> in Header
```

```
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
E248            Order Sequence Error <211> -> <213>; Expected Mandatory
Tag: <212> in Header
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 69 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E248            Order Sequence Error <212> -> <211>; Expected Mandatory
Tag: <213> in Header
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
E248            Order Sequence Error <211> -> <221>; Expected Mandatory
Tag: <212> in Header
W257            Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401            Unrecognized range formatin <222> in SEQID (0)
W401            Unrecognized range formatin <222> in SEQID (0)
E248            Order Sequence Error <222> -> <213>; Expected Mandatory
Tag: <400> in Header
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 88 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E248            Order Sequence Error <212> -> <211>; Expected Mandatory
Tag: <213> in Header
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
E248            Order Sequence Error <211> -> <213>; Expected Mandatory
Tag: <212> in Header
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 98 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E248            Order Sequence Error <212> -> <211>; Expected Mandatory
Tag: <213> in Header
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
E248            Order Sequence Error <211> -> <213>; Expected Mandatory
Tag: <212> in Header
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 108 contains 75-80 characters in tag
<400> and Sequence ID (0)
```

```
E310            Invalid sequence type in <212> in SEQID: (0)
E248            Order Sequence Error <212> -> <211>; Expected Mandatory
Tag: <213> in Header
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
E248            Order Sequence Error <211> -> <213>; Expected Mandatory
Tag: <212> in Header This error has occured more than 20 times, will not
be displayed
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 118 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 128 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 139 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 149 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 160 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 170 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
```

```
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 181 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 191 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W257            Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401            Unrecognized range formatin <222> in SEQID (0)
W401            Unrecognized range formatin <222> in SEQID (0)
W446            The current line: 203 contains 75-80 characters in tag
<222> and Sequence ID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 210 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 220 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 230 contains 75-80 characters in tag
<400> and Sequence ID (0)
E310            Invalid sequence type in <212> in SEQID: (0)
E202            Invalid input format; Value must be an integer in <211>
in SEQID (0)
W257            Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401            Unrecognized range formatin <222> in SEQID (0)
W401            Unrecognized range formatin <222> in SEQID (0)
W402            Undefined organism found in <213> in SEQ ID (0)
W446            The current line: 249 contains 75-80 characters in tag
```

<400> and Sequence ID (0)
E310 Invalid sequence type in <212> in SEQID: (0)
E202 Invalid input format; Value must be an integer in <211> in SEQID (0)
W402 Undefined organism found in <213> in SEQ ID (0)
E259 Found undefined lettercode; POS (33) SEQID(0)
W446 The current line: 260 contains 75-80 characters in tag <400> and Sequence ID (0)
E310 Invalid sequence type in <212> in SEQID: (0)
E202 Invalid input format; Value must be an integer in <211> in SEQID (0)
W402 Undefined organism found in <213> in SEQ ID (0)
W446 The current line: 271 contains 75-80 characters in tag <400> and Sequence ID (0) This error has occured more than 20 times, will not be displayed
E310 Invalid sequence type in <212> in SEQID: (0)
E202 Invalid input format; Value must be an integer in <211> in SEQID (0)
W402 Undefined organism found in <213> in SEQ ID (0) This error has occured more than 20 times, will not be displayed
E310 Invalid sequence type in <212> in SEQID: (0) This error has occured more than 20 times, will not be displayed
E202 Invalid input format; Value must be an integer in <211> in SEQID (0) This error has occured more than 20 times, will not be displayed
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401 Unrecognized range formatin <222> in SEQID (0)

W401 Unrecognized range formatin <222> in SEQID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W401 Unrecognized range formatin <222> in SEQID (0)
W401 Unrecognized range formatin <222> in SEQID (0) This error has occured more than 20 times, will not be displayed
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)
W257 Non-standard Feature Name/Key in <221> in SEQ ID (0)

The above error appear in the sequence listing is because, Working in project file is submitted for review. Please follow the instructions to generate the complete sequence listing file for review.

The submitted file is a PatentIn ".prj" (project) file which is only a work-in-progress file. The ".prj" file must be converted by PatentIn to the final “.txt” (ASCII text) file. Please follow the following steps to convert your .prj file to a properly formatted .txt file:

1) Please open the ".prj" file in PatentIn, and go to "Application Steps" on the PatentIn main menu.

2) Scroll down and click on "Generate Sequence Listing". Click on the "Start" tab; the sequences will be generated, and you should see "Successful completion" in the blank section above the "Start" tab.

3) Go to "Project" on the main PatentIn menu, and scroll down to "View/Print Sequence Listing". You will then be able to see the generated PatentIn text file: this will be in the required ASCII text file format, having a ".txt" file extension. That is the file to submit to the United States Patent and Trademark Office.

****

Validated By CRFValidator v 1.0.5

Application No: 15231687 Version No: 1.0

Input Set:

Output Set:

Started: 2016-10-21 14:04:58.158
Finished: 2016-10-21 14:05:11.865
Elapsed: 0 hr(s) 0 min(s) 13 sec(s) 707 ms
Total Warnings: 590
Total Errors: 813
No. of SeqIDs Defined: 0
Actual SeqID Count: 0

Error code		Error Description
E	248	Order Sequence Error <110> -> <110>; Expected Mandatory Tag: <120> in Header
E	248	Order Sequence Error <110> -> <110>; Expected Mandatory Tag: <120> in Header
E	248	Order Sequence Error <110> -> <110>; Expected Mandatory Tag: <120> in Header
E	248	Order Sequence Error <110> -> <110>; Expected Mandatory Tag: <120> in Header
E	248	Order Sequence Error <110> -> <110>; Expected Mandatory Tag: <120> in Header
E	248	Order Sequence Error <110> -> <110>; Expected Mandatory Tag: <120> in Header
E	248	Order Sequence Error <110> -> <110>; Expected Mandatory Tag: <120> in Header
E	248	Order Sequence Error <110> -> <110>; Expected Mandatory Tag: <120> in Header
E	287	Invalid WIPO ST.2 date format; Use (YYYY-MM-DD) in <141>
E	287	Invalid WIPO ST.2 date format; Use (YYYY-MM-DD)in <151>
E	248	Order Sequence Error <151> -> <213>; Expected Mandatory Tag: <210> in Header
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 59 contains 75-80 characters in tag <400> and
E	310	Invalid sequence type in <212> in SEQID: (0)
E	248	Order Sequence Error <212> -> <211>; Expected Mandatory Tag: <213> in Header

Input Set:

Output Set:

Started: 2016-10-21 14:04:58.158
Finished: 2016-10-21 14:05:11.865
Elapsed: 0 hr(s) 0 min(s) 13 sec(s) 707 ms
Total Warnings: 590
Total Errors: 813
No. of SeqIDs Defined: 0
Actual SeqID Count: 0

Error code		Error Description
E	202	Invalid input format; Value must be an integer in <211> in SEQID
E	248	Order Sequence Error <211> -> <213>; Expected Mandatory Tag: <212> in Header
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 69 contains 75-80 characters in tag <400> and
E	310	Invalid sequence type in <212> in SEQID: (0)
E	248	Order Sequence Error <212> -> <211>; Expected Mandatory Tag: <213> in Header
E	202	Invalid input format; Value must be an integer in <211> in SEQID
E	248	Order Sequence Error <211> -> <221>; Expected Mandatory Tag: <212> in Header
W	257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W	401	Unrecognized range formatin <222> in SEQID (0)
W	401	Unrecognized range formatin <222> in SEQID (0)
E	248	Order Sequence Error <222> -> <213>; Expected Mandatory Tag: <400> in Header
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 88 contains 75-80 characters in tag <400> and
E	310	Invalid sequence type in <212> in SEQID: (0)
E	248	Order Sequence Error <212> -> <211>; Expected Mandatory Tag: <213> in Header
E	202	Invalid input format; Value must be an integer in <211> in SEQID
E	248	Order Sequence Error <211> -> <213>; Expected Mandatory Tag: <212> in Header
W	402	Undefined organism found in <213> in SEQ ID (0)

Input Set:

Output Set:

Started: 2016-10-21 14:04:58.158
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Total Warnings: 590
Total Errors: 813
No. of SeqIDs Defined: 0
Actual SeqID Count: 0

Error code		Error Description
W	446	The current line: 98 contains 75-80 characters in tag <400> and
E	310	Invalid sequence type in <212> in SEQID: (0)
E	248	Order Sequence Error <212> -> <211>; Expected Mandatory Tag: <213> in Header
E	202	Invalid input format; Value must be an integer in <211> in SEQID
E	248	Order Sequence Error <211> -> <213>; Expected Mandatory Tag: <212> in Header
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 108 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	248	Order Sequence Error <212> -> <211>; Expected Mandatory Tag: <213> in Header
E	202	Invalid input format; Value must be an integer in <211> in SEQID
E	248	Order Sequence Error <211> -> <213>; Expected Mandatory Tag: <212> in Header This error has occured more than 20 times, will not be displayed
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 118 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 128 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID

Input Set:

Output Set:

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Actual SeqID Count: 0

Error code		Error Description
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 139 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 149 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 160 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 170 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 181 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID

Input Set:

Output Set:

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Finished: 2016-10-21 14:05:11.865
Elapsed: 0 hr(s) 0 min(s) 13 sec(s) 707 ms
Total Warnings: 590
Total Errors: 813
No. of SeqIDs Defined: 0
Actual SeqID Count: 0

Error code		Error Description
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 191 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W	401	Unrecognized range formatin <222> in SEQID (0)
W	401	Unrecognized range formatin <222> in SEQID (0)
W	446	The current line: 203 contains 75-80 characters in tag <222> and Sequence ID (0)
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 210 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 220 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 230 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID

Input Set:

Output Set:

Started: 2016-10-21 14:04:58.158
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Error code		Error Description
W	257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W	401	Unrecognized range formatin <222> in SEQID (0)
W	401	Unrecognized range formatin <222> in SEQID (0)
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 249 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
E	259	Found undefined lettercode; POS (33) SEQID(0)
W	446	The current line: 260 contains 75-80 characters in tag <400> and Sequence ID (0)
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0)
W	446	The current line: 271 contains 75-80 characters in tag <400> and Sequence ID (0) This error has occured more than 20 times, will not be displayed
E	310	Invalid sequence type in <212> in SEQID: (0)
E	202	Invalid input format; Value must be an integer in <211> in SEQID
W	402	Undefined organism found in <213> in SEQ ID (0) This error has occured more than 20 times, will not be displayed
E	310	Invalid sequence type in <212> in SEQID: (0) This error has occured more than 20 times, will not be displayed
E	202	Invalid input format; Value must be an integer in <211> in SEQID (0)

Input Set:

Output Set:

Started: 2016-10-21 14:04:58.158
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Elapsed: 0 hr(s) 0 min(s) 13 sec(s) 707 ms
Total Warnings: 590
Total Errors: 813
No. of SeqIDs Defined: 0
Actual SeqID Count: 0

Error code	Error Description
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 401	Unrecognized range formatin <222> in SEQID (0)
W 401	Unrecognized range formatin <222> in SEQID (0) This error has occured more than 20 times, will not be displayed
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)

Input Set:

Output Set:

Started: 2016-10-21 14:04:58.158
Finished: 2016-10-21 14:05:11.865
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Actual SeqID Count: 0

Error code	Error Description
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
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W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0)
W 257	Non-standard Feature Name/Key in <221> in SEQ ID (0) This error has occured more than 20 times, will not be displayed

Organization Applicant

      Street :
      City :
      State :
      Country :
      PostalCode :
      PhoneNumber :
      FaxNumber :
      EmailAddress :
<110> OrganizationName : Good Start Genetics, Inc.

Individual Applicant

      Street :
      City :
      State :
      Country :
      PostalCode :
      PhoneNumber :
      FaxNumber :
      EmailAddress :
<110> LastName : Porreca
<110> FirstName : Gregory
<110> MiddleInitial :
<110> Suffix :

Individual Applicant

      Street :
      City :
      State :
      Country :
      PostalCode :
      PhoneNumber :
      FaxNumber :
      EmailAddress :
<110> LastName : Laserson
<110> FirstName : Uri
<110> MiddleInitial :
<110> Suffix :

Application Project

<120> Title : METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
<130> AppFileReference : GSGE-002/04US 29258/78
<140> CurrentAppNumber : 15/231,687
<141> CurrentFilingDate : 2016-08-08

Earlier Applications

<150> PriorAppNumber : 13/266,862
<151> PriorFilingDate : 2012-03-13

Sequence

<213> OrganismName : Homo sapiens

<400> PreSequenceString :
tcacatcacc aagttaaaaa aaaaaarggg gcgggggggc agaatgaaaa tt 52
<212> Type : DNA
<211> Length : 52
SequenceName : 1
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaacaaggat gaattaagtt ttttttaaa aaagaaacat ttggtaaggg ga 52
<212> Type : DNA
<211> Length : 52
SequenceName : 2
SequenceDescription :

Feature

Sequence: 2:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atcaccaagt taaaaaaaaa aaagggrcgg gggggcagaa tgaaaattgc at 52
<212> Type : DNA
<211> Length : 52
SequenceName : 3
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctattgaacc agaaccaaac aggaatrcca tagcattttg taaactaaac tg 52
<212> Type : DNA
<211> Length : 52
SequenceName : 4
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
caggagttca agaccagcct actaaamcac acacacacac acacacacac ac 52
<212> Type : DNA
<211> Length : 52
SequenceName : 5
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gattaaataa tagtgtttat gtacccsgct tataggagaa gagggtgtgt gt 52
<212> Type : DNA
<211> Length : 52
SequenceName : 6
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
attgttatct tttcatataa ggtaacwgag gcccagagag attaaataac at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 7
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taattttaat taagtaaatt taattgrtag ataaataagt agataaaaaa ta 52
<212> Type : DNA
<211> Length : 52
SequenceName : 8
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtataaaaaa aaaaaaaaaa aaagttwgaa tgttttcttg cattcagagc ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 9
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atactaaaaa tttaaagttc tcttgcrata tattttctta atatcttaca tc 52
<212> Type : DNA
<211> Length : 52
SequenceName : 10
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgctgggatt acaggcgtga gccaccrcgc ctggcctgat gggacatatt tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 11
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ctacaatata agtatagtat tgcaaamcca tcaggaaggg tgttaactat tt 52
<212> Type : DNA
<211> Length : 52
SequenceName : 12
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gttgtctcca aacttttttt caggtgagaa ggtggccaac cgagcttcgg aaag 54
<212> Type : DNA
<211> Length : 54
SequenceName : 13
SequenceDescription :

Feature

Sequence: 13:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 29
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttttttcata aaagattata taaaggmtat tgcttttgaa tcacaaacac ta 52
<212> Type : DNA
<211> Length : 52
SequenceName : 14
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
atctagtgag cagtcaggaa agagaayttc cagatcctgg aaatcagggt ta 52
<212> Type : DNA
<211> Length : 52
SequenceName : 15
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens

<400> PreSequenceString :
tagagtataa aaaaaaaaaa aaaaaaagtt tgaatgtttt cttgcattca ga 52
<212> Type : DNA
<211> Length : 52
SequenceName : 16
SequenceDescription :

Feature

Sequence: 16:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgcaaatgcc aactatcaaa gatattsgag tatactgtca ataaacttca ta 52

<212> Type : DNA
<211> Length : 52
SequenceName : 17
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tcctcaacag ttagaaacaa tattttsagt gaittcccat gccaacttta ct 52

<212> Type : DNA
<211> Length : 52
SequenceName : 18
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttttggtat tgttgttaaa taagtgrgaa ttcaatacag tataatgtct gt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 19
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cttgaaatcg gatatatata tatatatgta tatatatata tatatatata tatatataca 60
tatatatata tagtattatc cctgttttca cagtttt 97
<212> Type : DNA
<211> Length : 97

SequenceName : 20
SequenceDescription :

Feature

Sequence: 20:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 72
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agaggggctg tgaaggacac caaggargag actaagagcc aggagggaaa ac 52

<212> Type : DNA
<211> Length : 52
SequenceName : 21
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tagagtttat tagcttttac tactctrctt agttactttg tgttacagaa ta 52

<212> Type : DNA
<211> Length : 52
SequenceName : 22
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
actagtgatg atgagcttct tttcatatgt ttgttggctg cataaatgtc ttc 53

<212> Type : DNA
<211> Length : 53
SequenceName : 23
SequenceDescription :

Feature

Sequence: 23:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens

<400> PreSequenceString :
gcagagaaaa gaggggctgt gaaggasacc aaggaggaga ctaagagcca gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 24
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttcagaggtc taccactggt gcatackcta atcacagtgt cgaaaatttt ac 52

<212> Type : DNA
<211> Length : 52
SequenceName : 25
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aagaaagagc aaaagagggc aaacttytca tacatttttg atgtcgaaac ca 52

<212> Type : DNA
<211> Length : 52
SequenceName : 26
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cctaaagttt aaaaagaaaa aaaaaaagga agaaggaatt aaaaatccaa ag 52

<212> Type : DNA
<211> Length : 52
SequenceName : 27
SequenceDescription :

Feature

Sequence: 27:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtgtgtgtgt gtatatatat atatatwtat atatttttt tttcctgagc ca 52

<212> Type : DNA

<211> Length : 52
SequenceName : 28
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aaactgttga tgttttcatt tatttasatc attggaaaac tttagattct ag 52
<212> Type : DNA
<211> Length : 52
SequenceName : 29
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttatccatt cttaaccaga acagacrttt tttcagagct ggtccaggaa aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 30
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttgaaatcgg atatatatat atatatrtat atatatatat atatatatat at 52
<212> Type : DNA
<211> Length : 52
SequenceName : 31
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tagtttttta tttcctcata ttattttcag tggctttttc ttccacatct tt 52
<212> Type : DNA
<211> Length : 52
SequenceName : 32
SequenceDescription :

Feature

Sequence: 32:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens

<400> PreSequenceString :
acatagttct cagtggtaca actacargtg atttctcttt tcttatttct gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 33
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
agagcaatgg catcccttgt cttgtgytat acaggatgca gcaatttata gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 34
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttctgtctac ataagatgtc atactaratt atcttttcca gcatgcattc ag 52

<212> Type : DNA
<211> Length : 52
SequenceName : 35
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cagggtggca tgttaggcag tgcttaraat aaatgagttg gttatacaag ta 52

<212> Type : DNA
<211> Length : 52
SequenceName : 36
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aggacacaca cacacacaca cacacacatg cacacacatt taaatagatg cat 53
<212> Type : DNA
<211> Length : 53
SequenceName : 37
SequenceDescription :

Feature

Sequence: 37:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 27

Other Information : May or may not be present
CDSJoin : No

Feature

Sequence: 37:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 28
Other Information : This region may or may not be present in its entirety
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
taaaaaattg gtataatgaa attgcayttg tagtctttgg acatttaaat cc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 38
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tttcaatact taagaggtac gcagagraaa gaggggctgt gaaggacacc aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 39
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cagcaatgaa tattttgagg ctgaggygct gaggggtaaa attgcagcct gg 52

<212> Type : DNA
<211> Length : 52
SequenceName : 40
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ttatggttta tatttttgtg tcttctcttt aacacatctt ttctagcaga attca 55

<212> Type : DNA
<211> Length : 55
SequenceName : 41
SequenceDescription :

Feature

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-------
Sequence: 41:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 30
      Other Information : This region may or may not be present in its entirety
      CDSJoin : No

Sequence
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<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtattttagt ttttttttt tgtttgtttt gttttgtttt gttttgtttt tg                52

<212> Type : DNA
<211> Length : 52
      SequenceName : 42
      SequenceDescription :

Feature
-------
Sequence: 42:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
      Other Information : May or may not be present
      CDSJoin : No

Sequence
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<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tgggtgactc catttttact tttagtytgg tctgttgagg cctcgtgaga ga                52

<212> Type : DNA
<211> Length : 52
      SequenceName : 43
      SequenceDescription :

Sequence
--------
<213> OrganismName : Homo sapiens
<400> PreSequenceString :
tattttcatg tattttagtt ttttttttt gtttgttttg ttttgttttg ttttg              55

<212> Type : DNA
<211> Length : 55
      SequenceName : 44
      SequenceDescription :

Feature
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Sequence: 44:
<221> FeatureKey : misc_feature
<222> LocationFrom : 27
<222> LocationTo : 30
      Other Information : This region may or may not be present in its entirety
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CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gtgtgtgtgt atatatatat atatatwtat attttttttt tcctgagcca aa 52

<212> Type : DNA
<211> Length : 52
SequenceName : 45
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
aacctattag catgtctggc agaaaaatag atacttaata aatttcttaa at 52

<212> Type : DNA
<211> Length : 52
SequenceName : 46
SequenceDescription :

Feature

Sequence: 46:
<221> FeatureKey : modified_base
<222> LocationFrom : 27
<222> LocationTo : 27
Other Information : May or may not be present
CDSJoin : No

Sequence

<213> OrganismName : Homo sapiens
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gaggcttaga cagtttaagt aactcargca tggttacaca actagctagg gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 47
SequenceDescription :

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<213> OrganismName : Homo sapiens
<400> PreSequenceString :
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<212> Type : DNA
<211> Length : 52
SequenceName : 48
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
gaaaccccac cccttctata gttttcyctt taatatttac aatggaacca tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 49
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
catatatata tagtgtgtgt gtgtgtrtat atatatatat atatatattt tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 50
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
cgagcgagag agagagagag agagagagga gccggcgcga gaactacgca tgc 53

<212> Type : DNA
<211> Length : 53
SequenceName : 51
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ggcaggtaat atctagtacc ttacttwtat ttcctgagca cattctacat tt 52

<212> Type : DNA
<211> Length : 52
SequenceName : 52
SequenceDescription :

Sequence

<213> OrganismName : Homo sapiens
<400> PreSequenceString :
ggccaggaat gggagtgctt aggtgcrgag gtggcactgt tcccgcagct gc 52

<212> Type : DNA
<211> Length : 52
SequenceName : 53

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

WITHDRAWAL NOTICE

OC000000086974701

Date Mailed: 11/07/2016

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 08/23/2016. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web. https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If the reply is not filed electronically via EFS-Web, the reply must be accompanied by a copy of the new notice.

If the Office previously granted a petition to withdraw the holding of abandonment or a petition to revive under 37 CFR 1.137, the status of the application has been returned to pending status.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/fstephanos/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

FORMALITIES LETTER

OC000000086974712

Date Mailed: 11/07/2016

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Filing Date Granted

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to comply with the sequence rules, 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR § 1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136.

- A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing." Applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). Refer to attachment or PAIR document dated 10/31/2016.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

For questions regarding compliance to these requirements, please contact:

- **For Rules interpretation, call (571) 272-2510**
- **For CRF submission help, call (571) 272-2510**
- **For PatentIn software program support technical assistance, call (866)217-9197.**
- **Send e-mail correspondence for PatentIn software program help to ebc@uspto.gov**
- **Patent software is available at http://www.uspto.gov/patents/resources/tools/checker/patentinrel.jsp .**

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

Petitioner Illumina, Inc., EX1003, p. 326

• A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Gregory Porreca
Uri Laserson

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/fstephanos/

Petitioner Illumina, Inc., EX1003, p. 327

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/231,687	08/08/2016	1634	800	GSGE-002/04US 29258/78	11	1

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

FILING RECEIPT

OC000000086974711

Date Mailed: 11/07/2016

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Gregory Porreca, Cambridge, MA;
Uri Laserson, Boston, MA;

Applicant(s)

Good Start Genetics, Inc., Cambridge, MA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/266,862 03/13/2012
which is a 371 of PCT/US10/01293 04/30/2010
which claims benefit of 61/182,089 05/28/2009
and claims benefit of 61/179,358 05/18/2009
and claims benefit of 61/178,923 05/15/2009
and claims benefit of 61/174,470 04/30/2009

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Petitioner Illumina, Inc., EX1003, p. 328

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/18/2016
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/231,687**
Projected Publication Date: Request for Non-Publication Acknowledged
Non-Publication Request: Yes
**********WARNING**********
Applicant has requested non-publication, certifying that the invention disclosed in this application has not been and will not be the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing; **and has also claimed** the benefit of an application filed in another country or under a multilateral agreement. Because the non-publication request and corresponding certification appears to be inconsistent with the priority claim, applicant is reminded that he/she has an obligation to promptly notify the Office and **rescind the non-publication request** if the invention disclosed in this application is the subject of an application filed in another country, or under a multilateral agreement, that requires eighteen-month publication.
**********WARNING**********
Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Petitioner Illumina, Inc., EX1003, p. 331

Electronic Acknowledgement Receipt

EFS ID:	27936062
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers
Filer Authorized By:	
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	30-DEC-2016
Filing Date:	08-AUG-2016
Time Stamp:	11:07:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Correspondence_11-07-2016_09_22_23.pdf	100472 39740c36457e7a1a6dfea693b6c2e9ce4dabe18d	no	2

Warnings:

Information:					
2	Sequence Listing	GSGE-002-04US_ST25.pdf	52411 6b138c1081b81b5e9b1faa9518a661e739449cb2	no	33
Warnings:					
Information:					
3	Response to Pre-Exam Sequence Notice	RESPONSE_TO_NOTICE_TO_COMPLY_WITH_REQUIREMENTS_FOR_PATENT_APPLICATIONS_CONTAINING_NUCLEOTI.pdf	22497 068252c89ed5cbc78a51c2dd31b9982fa440fa00	no	3
Warnings:					
Information:					
4	CRF Statement Paper and CRF are the same	STATEMENT_IN_SUPPORT_OF_COMPUTER_READABLE_FORM_SUBMISSION.pdf	15323 7d8f610a97c8a04a5d18d6ec7a86e55aa314655c	no	1
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Information:					
5	Sequence Listing (Text File)	GSGE-002-04US_ST25.txt	34047	no	-
Warnings:					
Information:					
		Total Files Size (in bytes):	224750		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

ENTERED IN CPI

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

FORMALITIES LETTER

OC000000086974712

Date Mailed: 11/07/2016

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Filing Date Granted

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to comply with the sequence rules, 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR § 1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136.

- A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing." Applicant must provide a substitute computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). Refer to attachment or PAIR document dated 10/31/2016.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

For questions regarding compliance to these requirements, please contact:

- **For Rules interpretation, call (571) 272-2510**
- **For CRF submission help, call (571) 272-2510**
- **For PatentIn software program support technical assistance, call (866)217-9197.**
- **Send e-mail correspondence for PatentIn software program help to ebc@uspto.gov**
- **Patent software is available at http://www.uspto.gov/patents/resources/tools/checker/patentinrel.jsp .**

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

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- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Gregory Porreca
  Uri Laserson

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/fstephanos/

Petitioner Illumina, Inc., EX1003, p. 335

GSGE-002-04US_ST25

SEQUENCE LISTING

<110> Good Start Genetics, Inc.
Porreca, Gregory
Laserson, Uri

<120> METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

<130> GSGE-002/04US 29258/78

<140> 15/231,687
<141> 2016-08-08

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Petitioner Illumina, Inc., EX1003, p. 342

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Petitioner Illumina, Inc., EX1003, p. 344

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<223> May or may not be present

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<223> This region may or may not be present in its entirety

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<210> 64
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<400> 64
aagaagaaaa ataaaaagaa agtgggycag accgagagaa caggaagcct ga 52

<210> 65
<211> 52
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<213> Homo sapiens

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aaggacaaag gcaaagagac aaaggckcaa cactgggggt ccccagagag tg 52

<210> 66
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<400> 66
tacctagtca cttcctgcct ccatggygca aaaggggatg ggtgtgcctc tt 52

<210> 67
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<212> DNA
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<400> 67
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<210> 68
<211> 52
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<213> Homo sapiens

<400> 68
ttctgactgg caaccagccc cactctytgg gagccctcag gaatgaactt gc 52

<210> 69
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<210> 70
<211> 52
<212> DNA
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<400> 70
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<210> 71
<211> 52
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<400> 71
aagcagccct ggggagtcgg ggcgggrcct ggattggaaa agagacggtc ac 52

<210> 72
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<212> DNA
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<400> 72
ctccaagttc tgggagcaga gtgtgcrgct aggctcctgg gatcgaggga tg 52

<210> 73
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<210> 74
<211> 52
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<400> 74
ctagtacctt acttccctca agttcawtca tctcacagat atttcctgag ca 52

<210> 75
<211> 52
<212> DNA
<213> Homo sapiens

<400> 75
aattagccgt gcgtggtggc gggtgcytgt aatcccacgt acttgggagg ct 52

<210> 76
<211> 52
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<400> 76
ccatggccag ccggggaggg gacgggmaca cacagaccca cacagagact ca 52

<210> 77
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<223> May or may not be present

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<400> 78
cgtagcagtt agcagatgat aggcggbgaa atcttatttc acagggcatt aa 52

<210> 79
<211> 52
<212> DNA
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<400> 79
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<210> 80
<211> 52
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<400> 80
cagatactgg ccctggtgac agtgggrctg tgcgtggggc cagagccttc tc 52

<210> 81
<211> 52
<212> DNA
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<400> 81
gacagatact ggccctggtg acagtgkggc tgtgcgtggg gccagagcct tc 52

<210> 82
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<212> DNA
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<211> 52
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<213> Homo sapiens

<400> 83
gtttcagacc agcctggcca acatagygaa accccatctc tactaaaaat aa 52

<210> 84
<211> 52
<212> DNA
<213> Homo sapiens

<400> 84
agtgggcgat tggatggagc tgagtayggg gcccatccag gctaatcaca cc 52

<210> 85
<211> 52
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<400> 85
ccgggctccg tgaatgtttg tcacatstct gaagaacgta tgaattacat aa 52

<210> 86
<211> 52
<212> DNA
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<400> 86
gaatcccaac cccgacgctc gtcgccsggc tccgtgaatg tttgtcacat gt 52

<210> 87
<211> 52
<212> DNA
<213> Homo sapiens

<400> 87
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<210> 88
<211> 52
<212> DNA
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<400> 88
tgggcagaag tcagggtcca aagaaakggc aaagaaaagt gtcagtggct ca 52

<210> 89
<211> 52
<212> DNA
<213> Homo sapiens

<400> 89
taagaaagac gtttttgatt tttttcrgac ttctctggct ccactaccct gc 52

<210> 90
<211> 52
<212> DNA
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<400> 90
ctgattcctg gccaggagcg gtggctyacg cctgtaatcc cagcgctttg gg 52

<210> 91
<211> 52
<212> DNA
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<400> 91
taaaaatgct gattcctggc caggagyggt ggctcacgcc tgtaatccca gc 52

<210> 92
<211> 52
<212> DNA
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<400> 92
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<210> 93
<211> 52
<212> DNA
<213> Homo sapiens

<400> 93
caagacctgt caaagatctg agaaatwtta cccgacttac aagctaacca tt 52

<210> 94
<211> 52
<212> DNA
<213> Homo sapiens

<400> 94
actgtaataa gtgctgtaaa agaaatrcac aaaataatat agcagagggt at 52

<210> 95
<211> 52
<212> DNA
<213> Homo sapiens

<400> 95
cttgaggtca ggagttcaag accagtytgg gcaacatggg gaaaaccttg tc 52

<210> 96
<211> 52
<212> DNA
<213> Homo sapiens

<400> 96
aggttgcagt gagccgagat catgccrttg cactccagcc ggggcaacaa aa 52

<210> 97
<211> 52
<212> DNA
<213> Homo sapiens

<400> 97
acaagtgtct tgaaattatc tgtgatytgc tatagagcaa tacttttgta aa 52

<210> 98
<211> 52
<212> DNA
<213> Homo sapiens

<400> 98
gtgggtatat gcagctctat gcactayctg ctcatttatt tggtaaatct aa 52

<210> 99
<211> 59
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(34)
<223> This region may or may not be present in its entirety

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<210> 100
<211> 52
<212> DNA
<213> Homo sapiens

<400> 100
agtctggagt gcaatggtgc aatctcrgct cactgcagcc tccacctccg gg 52

<210> 101
<211> 52
<212> DNA
<213> Homo sapiens

<400> 101
ctcctaatgg atatttccta aattttkctg aacagaattt aacttgagct gg 52

<210> 102
<211> 52
<212> DNA
<213> Homo sapiens

<400> 102
atttaaaaat ggatttctag aaaaacratc acatacttga atattttagc aa 52

<210> 103
<211> 52
<212> DNA
<213> Homo sapiens

<400> 103
ctataaatgg gtagcatgag ggattcragg aggtggctga aagaagcacg ta 52

<210> 104
<211> 52
<212> DNA
<213> Homo sapiens

<400> 104
aagaaaccaa gcatagtaga gtgttaraaa accaaagcaa ctaaacaact gt 52

<210> 105
<211> 52
<212> DNA
<213> Homo sapiens

<400> 105
cggggctcag aacttgtaac agaaaawtaa aatatactcc actcaaggga at 52

<210> 106
<211> 57
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (27)..(32)
<223> This region may or may not be present in its entirety

<400> 106
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<210> 107
<211> 63
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(38)
<223> This region may or may not be present in its entirety

<400> 107
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gcc 63

<210> 108
<211> 57
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(32)
<223> This region may or may not be present in its entirety

<400> 108
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<210> 109
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 109
gaggtggctg aaagaagcac gtatccctga tggcatggtt gcgggttata tg 52

<210> 110
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 110
gagaaaagca gttcctggaa caccccccacc ccttaacccc ttatctctgc tt 52

<210> 111
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 111

ttacatatgt atacatgtgc catgtttggt gtgccgcacc cattaactcg tc 52

<210> 112
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 112
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<210> 113
<211> 52
<212> DNA
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<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 113
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<210> 114
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<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 114
tactttaagt tttagggtac atgtgcacca tgtgcaggtt tgttacatat gt 52

<210> 115
<211> 52
<212> DNA
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<220>
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<223> May or may not be present

<400> 115
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<210> 116
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
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<400> 116
gtgcactaga attagctaaa gtgggggaaa aaaagatgca tttgatggtc ta 52

<210> 117
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 117
aacctccacc tcccaggttc aagagaattc tcctgcctca gcctcccaag ta 52

<210> 118
<211> 52
<212> DNA
<213> Homo sapiens

<400> 118
cctccctgtg atccgaagta gcagacrtac ttaacttcca tggtggattg tt 52

<210> 119
<211> 52
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<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 119
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<210> 120
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)

<223> May or may not be present

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<211> 53
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<213> Homo sapiens

<220>
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<400> 121
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<210> 122
<211> 52
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (27)..(27)
<223> May or may not be present

<400> 122
gaaggagaaa aagagaggaa ataagttaaa ataataaaca caattaataa ag 52

<210> 123
<211> 52
<212> DNA
<213> Homo sapiens

<400> 123
tgtatacatg tgccatgttg gtgtgcygca cccattaact cgtcatttag ca 52

<210> 124
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 124
tcacctgtca cctcctatag aactttcccc tgaccctcct ctatagcatt aa 52

<210> 125
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<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 125
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<210> 126
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 126
acagacatat ctacaaacac acttttttcac atatttgtgt aagtcattta tg 52

<210> 127
<211> 52
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<400> 127
aaagacaact aaactaacgc tcaatgmaaa aagtattcgc tgctgtttac at 52

<210> 128
<211> 52
<212> DNA
<213> Homo sapiens

<400> 128
taccgtgtac cccgtgtttg tgaatgmggc cgcatattac gaaaagaaag aa 52

<210> 129
<211> 52
<212> DNA
<213> Homo sapiens

<400> 129
cagggctgga ggtaaaacca tttattrcta accccagagc agtgaagaag tg 52

<210> 130
<211> 52
<212> DNA
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<400> 130
ttcttcattg cctattgaag agagagygga atgctttggt tgccagatat gg 52

<210> 131
<211> 52
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<213> Homo sapiens

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<210> 132
<211> 52
<212> DNA
<213> Homo sapiens

<400> 132
ttctgtgtaa catttcattt aagcaargga ttcggcaaat caaaaattgt ca 52

<210> 133
<211> 52
<212> DNA
<213> Homo sapiens

<400> 133
taaaacgtat tgaaggtatt attgackctg ttgaagcaaa gagaacaaaa ca 52

<210> 134
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<400> 134
atctgctctt ccagttggat gacaagyctt gctgtctaac acctgctgca ga 52

<210> 135
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<400> 135
ccatttttg ttgtattttt tttttcytga atacttttta tcgcagttgg tt 52

<210> 136
<211> 52
<212> DNA
<213> Homo sapiens

<400> 136
ccctgtctct aaaagaaaaa aaaaaaraaa aaaaaaagaa aacaaaaccc aa 52

<210> 137
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<400> 137
agtggctcca aaaaggtcat ggaaccyctt gaggatgatg caaattgact ct 52

<210> 138
<211> 52
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<213> Homo sapiens

<400> 138
taaagttact tttcttttat tgactttccc ttatttttta accttatgct tt 52

<210> 139
<211> 52
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (27)..(27)
<223> May or may not be present

<400> 139
cagagttaaa aaaaaaaaaa aaaaaaagga agtagcagca acagcttgga aa 52

<210> 140
<211> 52
<212> DNA
<213> Homo sapiens

<400> 140
gttgcccagg gttgagtgca gaggcayatc ttggctcaca gcaacctctg cc 52

<210> 141
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<213> Homo sapiens

<220>
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<210> 142
<211> 52
<212> DNA
<213> Homo sapiens

<400> 142
gcctacattc tgcaaagagg agggaasatt cacagctcca tacttgaacc ct 52

<210> 143
<211> 52
<212> DNA
<213> Homo sapiens

<400> 143

ccaaaggaga atagctctag gggaggsagg tggatgagta tgcatggggg ag 52

<210> 144
<211> 52
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (27)..(27)
<223> May or may not be present

<400> 144
gactccatct caaaaaaaaa aaaaaaatgc agtctaatgg cagaattaga ct 52

<210> 145
<211> 52
<212> DNA
<213> Homo sapiens

<400> 145
ttatttattt atttatttat ttttgaraca gggtctctgt tgtccaggct gg 52

<210> 146
<211> 52
<212> DNA
<213> Homo sapiens

<400> 146
ttttgaggca gggtctcact ctgttgycca gggttgagtg cagaggcaca tc 52

<210> 147
<211> 52
<212> DNA
<213> Homo sapiens

<400> 147
cgccttgcga aggccccaca gcttgcytgt gacaaacgtt cataggcaaa tg 52

<210> 148
<211> 52
<212> DNA
<213> Homo sapiens

<400> 148
ggaggtctgt acaaagcacc acctacytca tgggtcagtt tccacagcag aa 52

<210> 149
<211> 55
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(30)

<223> This region may or may not be present in its entirety

<400> 149
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<210> 150
<211> 52
<212> DNA
<213> Homo sapiens

<400> 150
aacatagtat ctaatatagc tttacaycca aagccaaaat atgaatacac tg 52

<210> 151
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 151
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<210> 152
<211> 52
<212> DNA
<213> Homo sapiens

<400> 152
cataccaaag ggcagctgga gggatayaga cggaagtcat gtggagagtg aa 52

<210> 153
<211> 52
<212> DNA
<213> Homo sapiens

<400> 153
caggtgtgag ccaccacgac caccaawtta gctcttttta ctccttccct tc 52

<210> 154
<211> 52
<212> DNA
<213> Homo sapiens

<400> 154
agtggtagct gattttgctt ctggatmctt tgccaccttc ccactcttta at 52

<210> 155
<211> 64
<212> DNA
<213> Homo sapiens

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<220>
<221> misc_feature
<222> (27)..(39)
<223> This region may or may not be present in its entirety

<400> 155
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acag 64

<210> 156
<211> 52
<212> DNA
<213> Homo sapiens

<400> 156
taaaaaatct ttcaatgagg agatgtyccc agagcaagac agctgtagga tg 52

<210> 157
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 157
aaaagaaaaa aaaaaaaaaa aaaaaaagaa aacaaaaccc aaacccataa ag 52

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<211> 52
<212> DNA
<213> Homo sapiens

<400> 158
cctgtctcta aaagaaaaaa aaaaaaraaa aaaaaagaaa acaaaaccca aa 52

<210> 159
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<212> DNA
<213> Homo sapiens

<220>
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<400> 159
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<210> 160
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 160
caggagctca tagaattaca tacaatcttt ttttttttt tttgagacag cg 52

<210> 161
<211> 55
<212> DNA
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<220>
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<223> This region may or may not be present in its entirety

<400> 161
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<210> 162
<211> 52
<212> DNA
<213> Homo sapiens

<400> 162
ccactaccac agtgcctaga gaacaayatg tgtttaataa tatttaaata at 52

<210> 163
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 163
ccctgtctct aaaagaaaaa aaaaaaaaaa aaaaaaagaa aacaaaaccc aa 52

<210> 164
<211> 52
<212> DNA
<213> Homo sapiens

<220>
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<222> (27)..(27)
<223> May or may not be present

<400> 164
ccattatatc attcatttcc cactcatttt cttcattcca accaagatat at 52

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	NOT YET ASSIGNED
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE DISCLOSURES

This paper is in response to the Notice mailed from the United States Patent and Trademark Office on November 7, 2016.

Applicants believe no fee is due with this response. Nevertheless, if any fee is required, Applicants authorize such fee to be taken out of Deposit Account No. 50-0369.

Amendments to the specification begin on page 2.

Remarks begin on page 3.

Amendments to the specification

Please amend page 1 of the specification by deleting the prior SEQUENCE LISTING section and replacing it with the following section:

SEQUENCE LISTING

This application contains a sequence listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. The ASCII-formatted sequence listing, created on December 29, 2016, is named GSGE-002-04US_ST25, and is 34,047 bytes in size.

Petitioner Illumina, Inc., EX1003, p. 370

Remarks

Applicant submits herewith a paper copy of the Sequence Listing, a copy of the Sequence Listing in computer readable form, an amendment specifically directing its entry into the application, and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written sequence listing and includes no new matter. No new matter is added.

Summary

Applicants submit that by this response, the informalities have been corrected and the application is complete and ready to be docketed for examination, an action that is respectfully requested. If there are any questions or comments concerning this response, the Examiners are invited and encouraged to contact Applicants' undersigned representative.

Dated: December 30, 2016

Respectfully submitted,
BROWN RUDNICK LLP

/Thomas C. Meyers/

Thomas C. Meyers, Reg. No. 36,989
Attorney for Applicant
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BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
Tel: 617-856-8483
Fax: 617-856-8201

Petitioner Illumina, Inc., EX1003, p. 371

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	NOT YET ASSIGNED
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

FILED ELECTRONICALLY

STATEMENT IN SUPPORT OF COMPUTER READABLE FORM SUBMISSION

I hereby state that the content of the paper copy and computer readable forms of the Sequence Listing, submitted in the above-identified application are the same. No new matter is added.

Dated: December 30, 2016

Respectfully submitted,
BROWN RUDNICK LLP

BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
Tel: (617) 856-8434
Fax: (617) 856-8201

/Thomas C. Meyers/
Thomas C. Meyers, Reg. No. 36,989
Attorney for Applicants
Email: tmeyers@brownrudnick.com

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 15231687 Document Date: 12/30/2016

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

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Sequence Listing was accepted.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Anjum, Durreshwar (CGI Federal)
Timestamp: [year=2017; month=1; day=11; hr=14; min=20; sec=40; ms=502; ]
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SEQUENCE LISTING

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Laserson, Uri

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

INFORMAL NOTICE

OC000000088495119

Date Mailed: 01/17/2017

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Gregory Porreca
  Uri Laserson

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/tnguyen/

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/231,687	08/08/2016	1634	800	GSGE-002/04US 29258/78	11	1

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

UPDATED FILING RECEIPT

OC000000088495118

Date Mailed: 01/17/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Gregory Porreca, Cambridge, MA;
Uri Laserson, Boston, MA;

Applicant(s)

Good Start Genetics, Inc., Cambridge, MA;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/266,862 03/13/2012
which is a 371 of PCT/US10/01293 04/30/2010
which claims benefit of 61/182,089 05/28/2009
and claims benefit of 61/179,358 05/18/2009
and claims benefit of 61/178,923 05/15/2009
and claims benefit of 61/174,470 04/30/2009

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Petitioner Illumina, Inc., EX1003, p. 396

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/18/2016
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/231,687**
Projected Publication Date: Request for Non-Publication Acknowledged
Non-Publication Request: Yes
**********WARNING**********
Applicant has requested non-publication, certifying that the invention disclosed in this application has not been and will not be the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing; **and has also claimed** the benefit of an application filed in another country or under a multilateral agreement. Because the non-publication request and corresponding certification appears to be inconsistent with the priority claim, applicant is reminded that he/she has an obligation to promptly notify the Office and **rescind the non-publication request** if the invention disclosed in this application is the subject of an application filed in another country, or under a multilateral agreement, that requires eighteen-month publication.
**********WARNING**********
Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Petitioner Illumina, Inc., EX1003, p. 397

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Petitioner Illumina, Inc., EX1003, p. 398

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Petitioner Illumina, Inc., EX1003, p. 399

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BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON MA 02111

MAILED
JAN 18 2017
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 15/231,687

1. THE REQUEST FILED August 8, 2016 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78	6709

21710 7590 01/31/2017

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
01/31/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Office Action Summary	Application No. 15/231,687	Applicant(s) PORRECA ET AL.	
	Examiner STEVEN POHNERT, Ph.D.	Art Unit 1634	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/8/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *68-78* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *68-78* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

DETAILED ACTION

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 69-70, drawn to identifying using unique differentiator tag, classified in C12Q 1/6874.

II. Claim 71-73, drawn to applying a common identifier tag, classified in C12Q 1/6827.

III. Claims 76-78, drawn to methods of genotyping or CNV analysis, classified in C12Q 1/6883.

3. Claim 68 and 74-75 link(s) inventions I, II, III. The restriction requirement among the linked inventions is **subject to** the nonallowance of the linking claim(s), claim 68 and 74-75. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions **shall** be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104 **Claims that require all the limitations of an allowable linking claim** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance,

whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, the allowable linking claim, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The inventions are distinct, each from the other because of the following reasons:

4. Inventions I and II are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed methods of identifying using a unique differentiate tag has a different design and outcome is not an obvious variant, or overlap in scope with methods of using a common identifier. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Searching identifying using a unique differentiate tag will not inherently provide art on methods of using a common identifier. Thus searching both would place a serious search burden on the office.

5. Inventions I and III are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed methods of identifying using a unique differentiate tag has a different design and outcome is not an obvious variant, or overlap in scope with methods of genotyping or CNV analysis. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Searching identifying using a unique differentiate tag will not inherently provide art on methods of genotyping or CNV analysis. Thus searching both would place a serious search burden on the office.

6. Inventions II and III are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed methods of requiring the use of a common identifier has a different design and effect, does not overlap in scope and is not an obvious variant of methods of genotyping or CNV analysis. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Searching identifying use of a common identifier will not inherently

provide art on methods of genotyping or CNV analysis. Thus searching both would place a serious search burden on the office.

7. Restriction for examination purposes as indicated is proper because all the inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN POHNERT, Ph.D. whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:00-5:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/STEVEN POHNERT/
Primary Examiner, Art Unit 1634
9.

Electronic Acknowledgement Receipt

EFS ID:	28204008
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers
Filer Authorized By:	
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	01-FEB-2017
Filing Date:	08-AUG-2016
Time Stamp:	12:36:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	29258-78_-_Porreca_Declaration.pdf	62452 e4f1eb54249a7a331ff964afc89fb3edde557089	no	1

Warnings:

Information:	
Total Files Size (in bytes):	62452

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [ ] The attached application, or
- [x] United States application or PCT international application number 15/231,687 filed on 08/08/2016

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

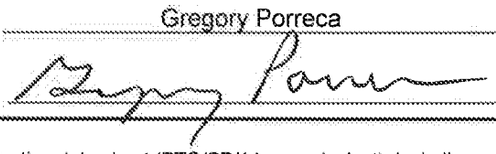
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Gregory Porreca Date (Optional): 1-27-17

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Acknowledgement Receipt	
EFS ID:	28798004
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers
Filer Authorized By:	
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	31-MAR-2017
Filing Date:	08-AUG-2016
Time Stamp:	14:53:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		29258_78_RR_Response.pdf	22229 7a96b4619cd41e0f7a900f668d7a01532a9f2b47	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	5
Warnings:			
Information:			
	Total Files Size (in bytes):	22229	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND ELECTION

This paper is in response to a Restriction Requirement mailed January 31, 2017, from the United States Patent and Trademark Office. Applicants believe no fee is due with this paper. Nevertheless, Applicants authorize any and all required fees due with this response to be charged to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 5.

Amendments to the claims

Please amend the claims as follows. The following listing of claims will replace all prior versions of claims in the application.

1-67. (Canceled)

68. (Previously Presented) A method for nucleic acid identification, the method comprising the steps of:

applying a unique differentiator tag to each member of a plurality of nucleic acid molecules obtained from a biological sample;

amplifying said nucleic acid molecules;

sequencing amplicons obtained in said amplifying step; and

identifying a sequence for said nucleic acid molecules.

69. (Previously Presented) The method of claim 68, wherein said identifying step comprises identifying said unique differentiator tags.

70. (Previously Presented) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon the number of said unique differentiator tags.

71. (Withdrawn) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

72. (Withdrawn) The method of claim 71, wherein said common identifier is used to identify a sample source.

Petitioner Illumina, Inc., EX1003, p. 415

73. (Withdrawn) The method of claim 72, wherein said common identifier is used to identify a patient.

74. (Previously Presented) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (Previously Presented) The method of claim 68, wherein said plurality of nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (Withdrawn) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

77. (Withdrawn) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

78. (Withdrawn) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

79. (New) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon the number of said unique differentiator tags.

80. (New) The method of claim 68, wherein said nucleic acid molecules are circulating tumor nucleic acid molecules.

Petitioner Illumina, Inc., EX1003, p. 416

81. (New) The method of claim 68, further comprising the step of determining the copy number of a genomic region or transcript in a patient from whom the sample is obtained.

82. (New) The method of claim 68, wherein said nucleic acid molecules are maternally-circulating fetal or placental nucleic acid molecules.

Petitioner Illumina, Inc., EX1003, p. 417

Remarks

In response to the Restriction Requirement, Applicants elect Invention I drawn to identifying nucleic acids using a unique differentiator tag. Applicants identify the claims encompassing the elected invention to be claims 68-70, 74, 75, and 79-82. The election is made without traverse. Claims 71-73 and 76-78 are withdrawn. Claims 79-82 are new. Support for the new claims is found in the application as-filed at page 7, second paragraph, and page 18, last paragraph, and page 19, first paragraph. No new matter is added.

Summary

If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative.

Dated: March 31, 2017

Respectfully submitted,
BROWN RUDNICK LLP

BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
Tel: (617) 856-8483
Fax: (617) 856-8201

/Thomas C. Meyers/
Thomas C. Meyers, Reg. No. 36,989
Attorney for Applicants
Email: tmeyers@brownrudnick.com

62734081 v1

Petitioner Illumina, Inc., EX1003, p. 418

Electronic Acknowledgement Receipt

EFS ID:	28956712
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Michelle Aiello
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	18-APR-2017
Filing Date:	08-AUG-2016
Time Stamp:	15:48:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	GSGE-POA-120413.pdf	104443 a7530b6564dcedbddfd8755401f74a0a27641121	no	1

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	GSGE-002-04US-Statement.pdf	24481 039c22a3931ad90eea4b0ef545154e9f5ddf1dea	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	128924	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 21710

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

■ The address associated with Customer Number: 21710

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address: Good Start Genetics, Inc.
237 Putnam Avenue
Cambridge, MA 02139

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Gregory J. Porreca	Date	12-4-2013
Name	Gregory J. Porreca	Telephone	617-714-0855
Title	Vice President of Research and Techology		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Good Start Genetics, Inc.

Application No./Patent No.: 15/231,687 Filed/Issue Date: August 8, 2016

Titled: METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Good Start Genetics, Inc. (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 042010 , Frame 0781 , or for which a copy thereof is attached.

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____
      The document was recorded in the United States Patent and Trademark Office at
      Reel _____ , Frame _____ , or for which a copy thereof is attached.

   2. From: _____ To: _____
      The document was recorded in the United States Patent and Trademark Office at
      Reel _____ , Frame _____ , or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Thomas C. Meyers/	April 18, 2017
Signature	Date
Thomas C. Meyers	36,989
Printed or Typed Name	Title or Registration Number

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

POA ACCEPTANCE LETTER

OC000000090778501

Date Mailed: 04/24/2017

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/18/2017.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ytdemisse/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78	6709

21710 7590 06/06/2017

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
06/06/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Office Action Summary	Application No. 15/231,687	Applicant(s) PORRECA ET AL.	
	Examiner STEVEN POHNERT, Ph.D.	Art Unit 1634	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/31/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *68-82* is/are pending in the application.

5a) Of the above claim(s) *71-73 and 76-78* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *68-70,74,75 and 79-82* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *8/8/2016* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Election/Restrictions

2. Applicant's election without traverse of group I, claims 68-70, 74-75, 79-82 in the reply filed on 3/31/2017 is acknowledged.

Claims 71-73, 76-78 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/31/2017.

Priority

The instant application was filed 08/08/2016 is a continuation of 13266862, filed 03/13/2012 and is a national stage entry of PCT/US10/01293 , International Filing Date: 04/30/2010, claims priority from provisional application 61182089, claims priority from provisional application 61179358, filed 05/18/2009, claims priority from provisional application 61178923, filed 05/15/2009, and priority from provisional application 61174470, filed 04/30/2009.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 8/11/2016 is being considered by the examiner.

Claim Objections

4. Applicant is advised that should claim 70 be found allowable, claim 79 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

5. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 68-70, 74-75, 79-82 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The Board has held, “If a claim is amenable to two or more plausible constructions, applicant is required to amend the claim to more precisely define the metes and bounds of the claimed invention or the claim is indefinite under §112, ¶2.” Ex parte Miyazaki, 89 USPQ2d 1207 (BPAI 2008) (expanded panel).

The US Supreme Court in NAUTILUS, INC. v. BIOSIG INSTRUMENTS, INC. (2014) held, “we hold that a patent is invalid for indefiniteness if its claims, read in light

of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention."

Claim 68 recites, "unique differentiator tag." The recitation of unique is a relative term which inherently suggests there are non-unique. Merriam –webster.com (https://www.merriam-webster.com/dictionary/unique, 5/30/2017) defines unique as

Definition of UNIQUE

1 :
being the only one
:
SOLE „ his *unique* concern was his own comfort
- I can't walk away with a *unique* copy. Suppose I lost it? — Kingsley Amis
- the *unique* factorization of a number into prime factors

2 a
:
being without a like or equal
:
UNEQUALED
- could stare at the flames, each one new, violent, *unique* — Robert Coover

b
:
distinctively characteristic
:
PECULIAR 1
- this is not a condition *unique* to California — Ronald Reagan

3 :
UNUSUAL „ a very *unique* ball-point pen
- we were fairly *unique*, the sixty of us, in that there wasn't one good mixer in the bunch — J. D. Salinger

Thus it is unclear if the recitation of unique requires the sequence is merely not found in the sample, does not occur naturally in any known genome, or occurs only in a single copy on the probe. Thus it is unclear if unique requires the sequence does not occur anywhere else ever, including other tags in another copy of a kit, or merely excludes the unique differentiator tag sequence to not occur in the sequence being examined.

Claims 69-70, 74-75, 79-82 are rejected as they depend from claim 68.

Claim Rejections - 35 USC § 102

7. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

8. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim(s) 68-6974-75, 81 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10)..

With regards to claim 68, Pourmand teaches

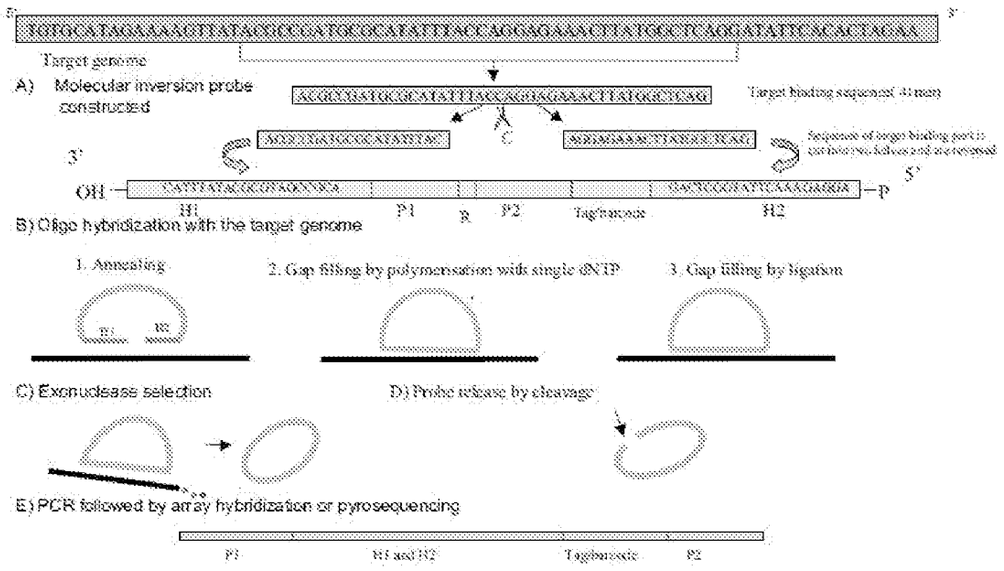


Figure 1

Poumard teaches, “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, “We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60℃, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, “MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.”(page 2, column 1, 1st full paragraph).

Claim Rejections - 35 USC § 103

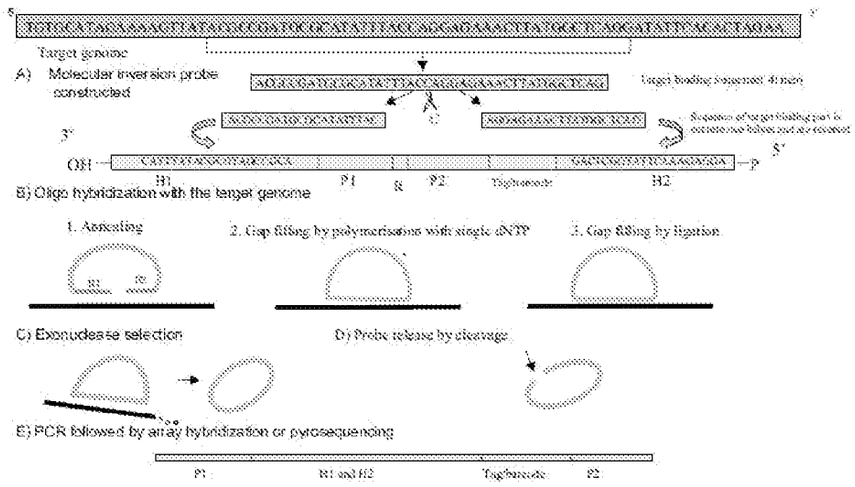
10. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

11. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 68-70, 74-75, 79, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Meyer (Nature Protocoles (2008) volume 3, pages 267-278, epublished Jan 31, 2008).

With regards to claim 68, Pourmand teaches



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Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, “We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, “MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.”(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach determining presence of sequencing or amplification errors.

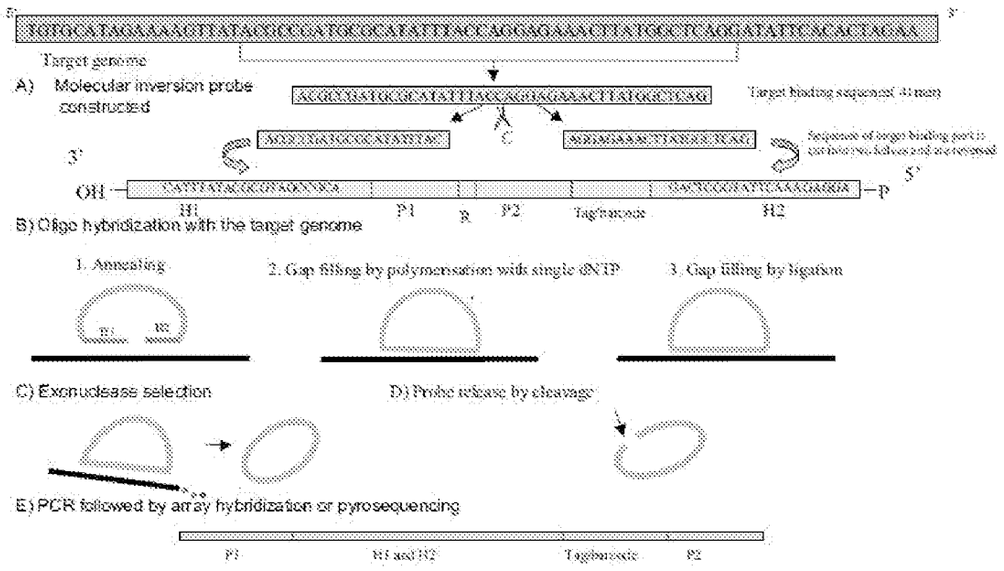
However, Meyer teaches preparing batches of barcoded nucleic acids (unique tags) by attaching barcodes or sequence tags to nucleic acids. See p. 271, Box 1;

Quality control and Procedure. The barcodes are added to purified PCR products or positive control PCR products (p. 272, Reagent Setup; p. 273, step 10). The batches are pooled and sequenced in parallel. A contamination in a batch of barcodes is determined by determining a frequency at which cross-contamination of adapters occurred during synthesis or dilution. Meyer further teaches a formula that takes into account and estimates false assignment that occurs due to sequencing errors and cross-contamination of barcoding adapters during synthesis and dilution (Box 1). Therefore, Meyer teaches identifying a contamination in a batch of barcodes (unique tags)by determining a frequency at which an incorrect adapter sequence occurs in the batches.

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis.

13. Claim 68-69, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) amd Shoemaker (US20080090239 published 4/17/2008).

With regards to claim 68, Pourmand teaches



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With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, “We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60℃, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, “MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.”(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach use of nucleic acids from circulating tumors or fetal nucleic acids.

However, Shoemaker teaches, “[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large number of maternal cells in the blood which make the analysis time consuming and prone to error.”

Shoemaker teaches, “0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying, quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc.”

Shoemaker teaches, “In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods, which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep

sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detecting circulating tumor nucleic acids or circulating fetal nucleic acids in the method of Poumard. The artisan would be motivated to use methods that are less invasive methods than aminocentesis or tumor biopsy. The artisan would have a reasonable expectation of success as the artisan is merely using known samples in known methods.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*,

686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

15. Claims 68-70, 74-75, 79-82 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending

Application No. 13/266,862 in view of Pourmand (BMC informatics (2006) volume 7:500, pages 1-10). This is a provisional nonstatutory double patenting rejection.

Claim 1 of '862 is drawn to A method for analyzing a target nucleic acid, the method comprising:providing a sample comprising a target nucleic acid;contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes, each different molecular inversion probe comprising:a 5' region comprising a 5' terminal nucleotide;a 3' region comprising a 3' terminal nucleotide; anda central region flanked by the 5' region and the 3' region;wherein the 5' region ~~re-~~is complementary to anucleic acid residueflanking ~~the-~~a 3' end of one of a plurality of subregions of the target nucleic acid and the 3' region is complementary to a nucleic acid residue flanking a 5' end of the subregion;wherein each subregion is different and overlaps with at least one other subregion; andwherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence;wherein when hybridized to the target nucleic acid in a circular configuration, the 5' terminal nucleotide and the 3' terminal nucleotide of each probe are separated by a plurality of nucleotides on the target nucleic acid; converting hybridized probes into closed circularized probes;isolating a plurality of circularized probes having nucleic acid sequences of different subregions; and analyzing the isolated subregions.

Claim 13 of ‘862 teach, “wherein the obtaining comprises capturing target nucleic acids from a genomic sample of the subject with molecular inversion probes, each comprising a unique differentiator tag sequence.”

Claims of ‘862 do not specifically teach amplifying.

However, Pourmand teaches

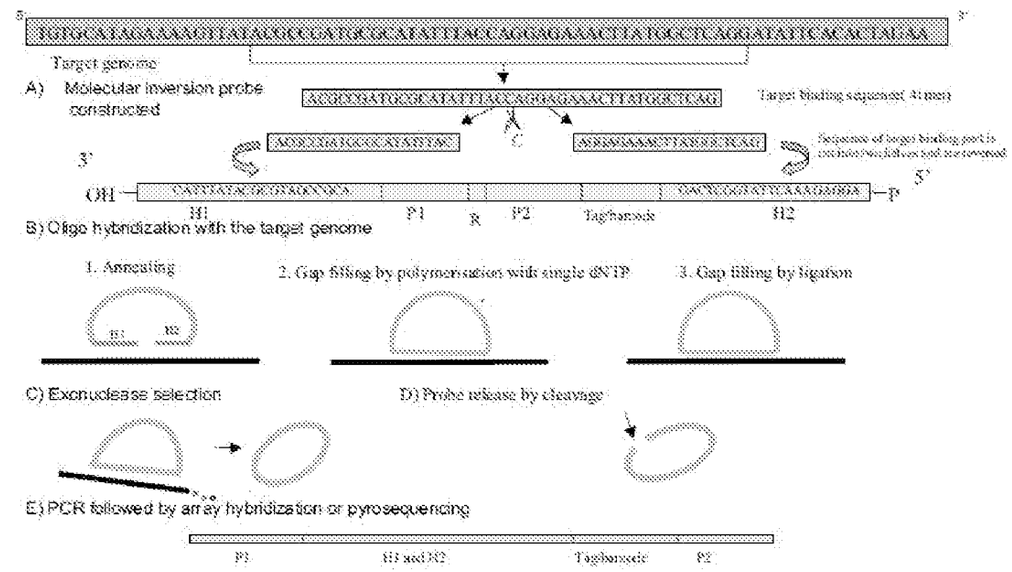

Figure 1

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With regards to claim 74-75, Poumard teaches, “We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60℃, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, “MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.”(page 2, column 1, 1st full paragraph).

Other dependent claims are obvious variants of the methods of Pourmand and ‘862.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to improve the molecular inversion probe method of '862 with unique differentiator tags with amplifying and sequencing of Poumard. The artisan would be motivated to amplify and sequence the molecular inversion probes to increase the amount of nucleic acid being detected and thus increase the sensitivity by an art . The artisan would have a reasonable expectation of success as the artisan is merely be using art accepted methods of analysis of nucleic acid sequences using molecular inversion probes.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN POHNERT, Ph.D. whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:00-5:00, every second Friday off.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/STEVEN POHNERT/
Primary Examiner, Art Unit 1634

Notice of References Cited	Application/Control No. 15/231,687	Applicant(s)/Patent Under Reexamination PORRECA ET AL.	
	Examiner STEVEN POHNERT, Ph.D.	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-2008/0090239 A1	04-2008	SHOEMAKER; DANIEL	G01N33/5091	435/6.12
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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Petitioner Illumina, Inc., EX1003, p. 447

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2016-08-11
Name/Print	Thomas C. Meyers	Registration Number	36,989

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Name/Print	Thomas C. Meyers	Registration Number	36,989

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(Not for submission under 37 CFR 1.99)

Application Number	15231687
Filing Date	2016-08-08
First Named Inventor	Gregory Porreca
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	GSGE-002/04US 29258/78

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	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

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	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

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	Attorney Docket Number	GSGE-002/04US 29258/78

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	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

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	41	European Search Report for EP app. no. 10770071.8
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	44	International Search Report and Written Opinion for WO 2010/126614

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	First Named Inventor	Gregory Porreca
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	GSGE-002/04US 29258/78

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EFS ID:	30288332
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Benjamin Maggin
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	06-SEP-2017
Filing Date:	08-AUG-2016
Time Stamp:	17:52:13
Application Type:	Utility under 35 USC 111(a)

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1		GSGE-002-04US-Response-to-NFOA.pdf	28563 c644f09e1404cd192af4484a20aaef7c77b8d531	yes	8

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	Applicant Arguments/Remarks Made in an Amendment	5	8
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

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RESPONSE

This paper is in response to a non-final office action mailed June 6, 2017, from the United States Patent and Trademark Office. Applicants believe no fee is due with this paper. Nevertheless, Applicants authorize any and all required fees due with this response to be charged to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 5.

Amendments to the claims

Please amend the claims as follows. The following listing of claims will replace all prior versions of claims in the application.

1-67. (Canceled)

68. (Currently Amended) A method for nucleic acid identification, the method comprising the steps of:

applying a unique differentiator tag to each member of a plurality of nucleic acid molecules obtained from a biological sample, wherein each unique differentiator tag is distinct from any other unique differentiator tag;

amplifying said nucleic acid molecules;

sequencing amplicons obtained in said amplifying step; and

identifying a sequence for said nucleic acid molecules.

69. (Previously Presented) The method of claim 68, wherein said identifying step comprises identifying said unique differentiator tags.

70. (Previously Presented) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon the number of said unique differentiator tags.

71. (Withdrawn) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

Petitioner Illumina, Inc., EX1003, p. 503

72. (Withdrawn) The method of claim 71, wherein said common identifier is used to identify a sample source.

73. (Withdrawn) The method of claim 72, wherein said common identifier is used to identify a patient.

74. (Previously Presented) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (Previously Presented) The method of claim 68, wherein said plurality of nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (Withdrawn) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

77. (Withdrawn) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

78. (Withdrawn) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

79. (Canceled)

80. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are circulating tumor nucleic acid molecules.

81. (Previously Presented) The method of claim 68, further comprising the step of determining the copy number of a genomic region or transcript in a patient from whom the sample is obtained.

82. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are maternally-circulating fetal or placental nucleic acid molecules.

Petitioner Illumina, Inc., EX1003, p. 505

Remarks

Claims 68-70, 74, 75, and 80-82 are pending in the application. Claim 68 is amended and claim 79 is canceled. Support for the amendment is found in the specification as-filed at paragraphs [0023]-[0025]. No new matter is added.

Claim Objection

The Office Action states that claim 79 is improper for being a substantial duplicate of claim 70. Claim 79 is hereby canceled. Applicant submits that the claim objection is thus overcome.

Rejections under 35 U.S.C. §112

The office action rejects claims 68-70, 74, 75, and 79-82 under 35 U.S.C. §112 as being indefinite for the recitation of unique differentiator tags. As discussed in greater detail below, claim 68 is amended to clarify the nature of the unique differentiator tags, and accordingly Applicant believes the §112 rejection is overcome.

Rejections under 35 U.S.C. §102

The office action states that claims 68, 69, 74, 75, and 81 are rejected under 35 U.S.C. §102(b) over Pourmand (BMC Informatics, 2006, 7:500). Applicant disagrees.

In order to anticipate a claim, the Patent Office requires that a single prior art reference teach each and every element of the claim. MPEP §2131. Pourmand fails to show applying a distinct and unique differentiator tag to each member of a plurality of nucleic acid molecules.

Claimed methods use tags to uniquely identify individual molecules and follow them through the amplification reaction. Those methods therefore allow starting molecules to be followed and distinguished from each other in order to overcome bias and errors associated with genome capture, amplification, and sequencing. *See published application, paragraph [0023].* In

contrast to Applicant's approach, Pourmand discloses tagging groups of like sequence for ensemble detection. Pourmand's disclosure would be useless for following individual molecules and/or distinguishing individual nucleic acids strands from each other.

Pourmand reports methods for designing barcoded molecular inversion probes (MIPs) for SNP detection, as was commonplace prior to the present disclosure. *See Pourmand, page 4, first column, last paragraph, through second column, first paragraph.* The barcodes as reported by Pourmand can distinguish categories of SNPs, but cannot distinguish individual starting molecules. *Id., page 2, left column.* Pourmand simply applies tags, amplifies, and then observes the relative numbers of one SNP versus another. Unlike the claimed methods, Pourmand's method of ensemble averaging does not distinguish one starting molecule from another, and therefore does not address amplification bias. Pourmand's method merely allows groups of molecules—not individual molecules—to be distinguished.

Although Pourmand does not show the required claim element of applying a unique differentiator tag to each member of a plurality of nucleic acid molecules, to further clarify the distinction, the claims are amended to specify that the unique differentiator tag applied to each nucleic acid molecule is different from all of the other unique differentiator tags. That feature is not disclosed or suggested in Pourmand, which is limited to applying unique probes for each genotype.

Since Pourmand does not anticipate the present claims, Applicant submits that the §102 rejection should be withdrawn.

Rejections under 35 U.S.C. §103

The office action states that claims 68-70, 74, 75, 79, and 81 are rejected under 35 U.S.C. §103 over Pourmand in view of Meyer (Nat. Prot., 2008, 3:267-78). The office action states that claims 68-69, 74, 75, and 81 are rejected under 35 U.S.C. §103 over Pourmand in view of

Shoemaker (US 2008/0090239). Applicant submits that the claims are not obvious over any combination of those references.

In order to establish a prima facie case of obviousness, the prior art must provide motivation to modify a reference or to combine multiple references in a manner that would lead one of ordinary skill in the art to an applicant's claimed invention with a reasonable expectation of success. *See e.g., KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); and MPEP § 2143. Furthermore, an obviousness rejection cannot be established unless each claim element is disclosed in the cited art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Without a reference disclosing the missing claim elements, there can be no motivation of achieving the claimed invention or likelihood of success in doing so. *See Wyers v. Master Lock Co.*, 616 F.3d 1231 (Fed. Cir. 2010) (providing a prima face case requires a teaching or suggestion of all claim limitations along with an apparent reason to combine the references).

As discussed in the section above, Pourmand fails to disclose each and every claim element. Meyer and Shoemaker do not make up for what Pourmand lacks. Meyer merely reports a molecular barcoding method for sequencing multiple samples on the 454 platform. *See Meyer, Abstract.* But Meyer does not disclose using MIPs to uniquely tag and distinguish template molecules. Shoemaker reports the use of nucleic acids from circulating tumor samples and fetal samples. *Shoemaker, paragraph [0004].* Shoemaker does not disclose or suggest applying a unique differentiator tag to each molecule in order to distinguish the starting molecules in the assay. Like Pourmand, neither Meyer nor Shoemaker discloses the element of the unique differentiator tag applied to each nucleic acid molecule being different from the unique differentiator tag applied to every other nucleic acid molecule. Accordingly, no combination of those references makes the present claims obvious.

Applicant submits that the §103 rejection is overcome and should be withdrawn.

Double Patenting

Claims 68-70, 74, 75, and 79-82 are provisionally rejected on the ground of nonstatutory double patenting over claim 1 of copending application no. 13/266,862 in view of Pourmand. Since the rejection is provisional, Applicant requests that it be held in abeyance.

Summary

If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative.

Dated: September 6, 2017

Respectfully submitted,
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62866104 v2

Petitioner Illumina, Inc., EX1003, p. 509

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EFS ID:	30458242
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [ ] The attached application, or
- [x] United States application or PCT international application number 15/231,687 filed on 08/08/2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

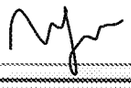
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Uri Laserson Date (Optional):

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78	6709

21710 7590 10/27/2017

BROWN RUDNICK LLP
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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
10/27/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Office Action Summary	Application No. 15/231,687	Applicant(s) PORRECA ET AL.	
	Examiner STEVEN POHNERT, Ph.D.	Art Unit 1634	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/6/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *68-78 and 80-82* is/are pending in the application.

5a) Of the above claim(s) *71-73 and 76-78* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *68-70,74,75 and 80-82* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *8/8/2016* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Claim Status and Formal matters

This action is in response to papers filed 9/6/2017.

Claims 68 has been amended. The response asserts can be found in paragraphs 0023-0025, however the specification as filed has no paragraph numbers.

Applicant's election without traverse of group I, claims 68-70, 74-75, 80-82 in the reply filed on 3/31/2017 is acknowledged.

Claims 71-73, 76-78 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/31/2017.

Claim 79 has been canceled. Thus the objection to claim 79 has been withdrawn.

Priority

The instant application was filed 08/08/2016 is a continuation of 13266862, filed 03/13/2012 and is a national stage entry of PCT/US10/01293 , International Filing Date: 04/30/2010, claims priority from provisional application 61182089, claims priority from provisional application 61179358, filed 05/18/2009, claims priority from provisional

application 61178923, filed 05/15/2009, and priority from provisional application 61174470, filed 04/30/2009.

Information Disclosure Statement

1. The information disclosure statements (IDS) submitted on 8/11/2016 is being considered by the examiner.

Specification

2. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 1 has been amended to recite, "wherein each unique differentiator tag is distinct from any other unique differentiator tag." The response asserts can be found in paragraphs 0023-0025, however the specification as filed has no paragraph numbers. Review and searching of the specification does not recite "distinct."

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 68-78, 80-82 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended to recite, “wherein each unique differentiator tag is distinct from any other unique differentiator tag.” The response asserts can be found in paragraphs 0023-0025, however the specification as filed has no paragraph numbers. Review and searching of the specification does not recite “distinct.“ Page 8 of the specification teaches, " . In some embodiments, the methods further comprising determining a statistical confidence for thegenotype based on the number of unique combinations of target nucleic acid and differentiator tag sequences.”.

Page 42 of the specification teaches, “According to some aspects, a library of preparative nucleic acid molecules (e.g., MIPs, each nucleic acid in the library having a unique differentiator tag sequence, maybe constructed such that the number of nucleic acid molecules in the library is significantly larger than the number prospective target nucleic acid molecules to be captured using the library. This ensures that products of the preparative methods include only unique target:differentiator tag sequence; e.g., in a MIP reaction the capture step would undersample the total population of unique differentiator tag sequences in the MIPlibrary. For example, an experiment utilizing 1 g of genomic DNA will contain about -150,000 copies of a diploid genome. For a MIP

library, each MIP in the library comprising a randomly produced 12-mer differentiator tag sequence (-1.6 million possible unique differentiator tag sequences), there would be more than 100 unique differentiator tag sequences per genomic copy. For a MIP library, each MIP in thelibrary comprising a randomly produced 15-mer differentiator tag sequence (-~1 billion possible unique differentiator tag sequences), there would be more than 7000 unique differentiator tag sequences per genomic copy. Therefore, the probability of the same differentiator tag sequence being incorporated multiple times is incredibly small. Thus, it is to be appreciated that the length of the differentiator tag sequence is to be selectedbased on the amount of target sequence in a MIP capture reaction and the desired probability for having multiple, independent occurrences of target:differentiator tag sequence combinations."

Thus the amendment has introduced new matter.

Response to Arguments

This is a new ground of rejection necessitated by amendment.

Claim Rejections - 35 USC § 102

5. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

6. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim(s) 68-69, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10)..

With regards to claim 68, Pourmand teaches

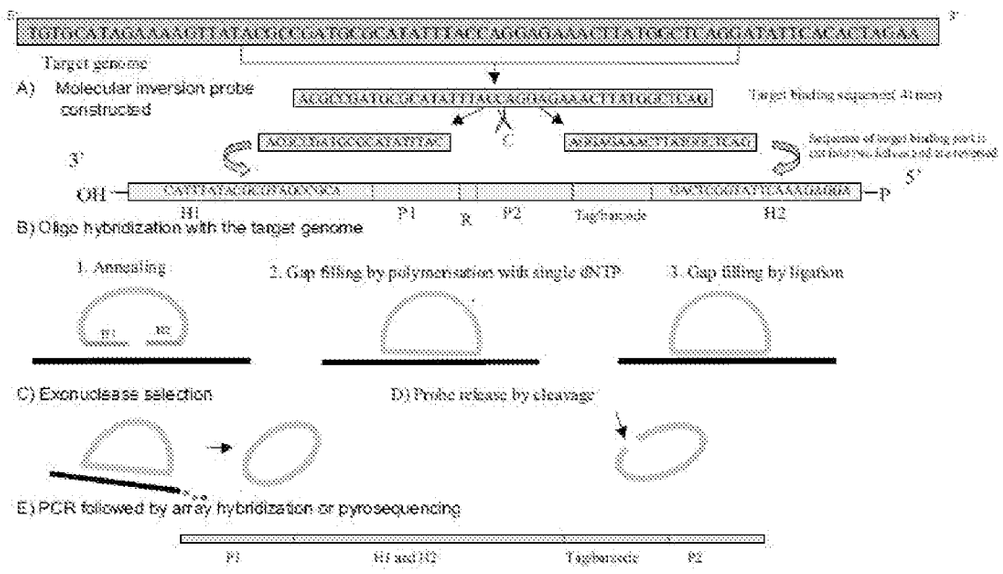


Figure 1

Poumard teaches, “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and

identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, “We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60℃, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, “MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.”(page 2, column 1, 1st full paragraph).

Response to Arguments

The response traverses the rejection asserting, “Claimed methods use tags to uniquely identify individual molecules and follow them through the amplification reaction. Those methods therefore allow starting molecules to be followed and distinguished from each other in order to overcome bias and errors associated with genome capture, amplification, and sequencing. See published application, paragraph [0023]..” This argument has been thoroughly reviewed but is not considered persuasive as the claims provide no specific limitations which differentiate the instant claims methods from those of Porumand. Further, the instant application has not been published.

The response further asserts, “In contrast to Applicant's approach, Pourmand discloses tagging groups of like sequence for ensemble detection. Pourmand's disclosure would be useless for following individual molecules and/or distinguishing individual nucleic acids strands from each other.” This argument has been thoroughly reviewed but is not considered persuasive as Pourmand teaches “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a

universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

The response continues by asserting, "The barcodes as reported by Pourmand can distinguish categories of SNPs, but cannot distinguish individual starting molecules. Id., page 2, left column." This argument has been thoroughly reviewed but is not considered persuasive as the response is arguing limitations that are not specific to the claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., cannot distinguish individual starting molecules. Id., page 2, left column) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further Pourmand teaches," A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or

cleavage site. (page 2, 2nd column). Thus Pourmand could distinguish starting molecules.

The response further asserts, “Although Pourmand does not show the required claim element of applying a unique differentiator tag to each member of a plurality of nucleic acid molecules, to further clarify the distinction, the claims are amended to specify that the unique differentiator tag applied to each nucleic acid molecule is different from all of the other unique differentiator tags.” This argument has been thoroughly reviewed but is not considered persuasive as Pourmand , “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus the rejection is maintained.

Claim Rejections - 35 USC § 103

8. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of

rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

9. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 68-70, 74-75, 79, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Meyer (Nature Protocoles (2008) volume 3, pages 267-278, epublished Jan 31, 2008).

With regards to claim 68, Pourmand teaches

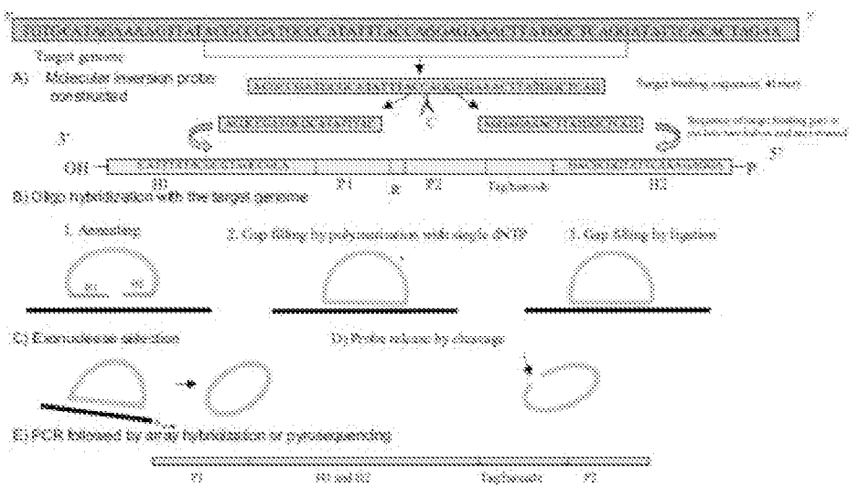


Figure 1

Poumard teaches, “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are

homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, “We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60℃, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical

studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, “MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.”(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach determining presence of sequencing or amplification errors.

However, Meyer teaches preparing batches of barcoded nucleic acids (unique tags) by attaching barcodes or sequence tags to nucleic acids. See p. 271, Box 1; Quality control and Procedure. The barcodes are added to purified PCR products or positive control PCR products (p. 272, Reagent Setup; p. 273, step 10). The batches are pooled and sequenced in parallel. A contamination in a batch of barcodes is determined by determining a frequency at which cross-contamination of adapters occurred during synthesis or dilution. Meyer further teaches a formula that takes into account and estimates false assignment that occurs due to sequencing errors and cross-contamination of barcoding adapters during synthesis and dilution (Box 1). Therefore, Meyer teaches identifying a contamination in a batch of barcodes (unique tags)by determining a frequency at which an incorrect adapter sequence occurs in the batches.

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis. .

Response to Arguments

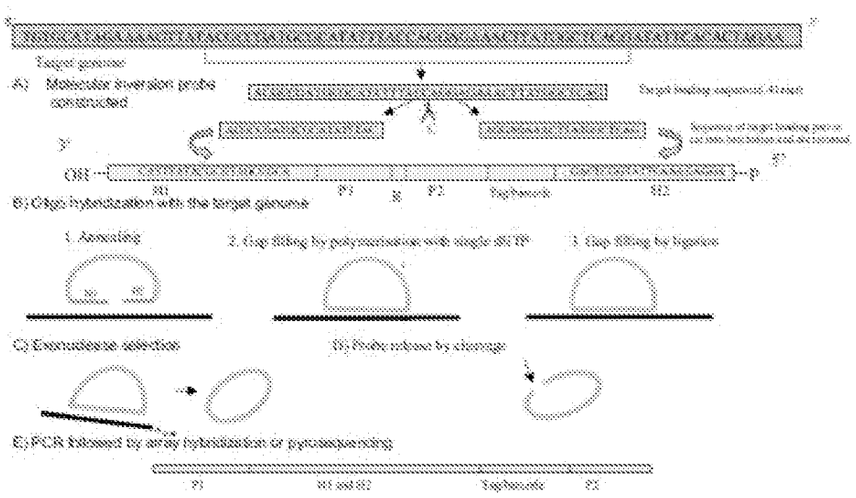
The response begins traversing the rejection by providing arguments with respect to motivation. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, the rejection states, "The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. "

The response asserts the art does not teach the use of unique tags. This argument is not persuasive as Pourmand , "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2,

that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

11. Claim 68-69, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) amd Shoemaker (US20080090239 published 4/17/2008).

With regards to claim 68, Pourmand teaches



T Figure 1

Poumard teaches, “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are

separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

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With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, “We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60℃, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical

tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, “MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.”(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach use of nucleic acids from circulating tumors or fetal nucleic acids.

However, Shoemaker teaches, “[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large number of maternal cells in the blood which make the analysis time consuming and prone to error.”

Shoemaker teaches, “0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying,

quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc."

Shoemaker teaches, "In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods, which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detecting circulating tumor nucleic acids or circulating fetal nucleic acids in the method of Poumard. The artisan would be motivated to use methods that are less invasive methods than aminocentesis or tumor biopsy. The artisan would have a reasonable expectation of success as the artisan is merely using known samples in known methods.

Response to Arguments

The response asserts the art does not teach the use of unique tags. This argument is not persuasive as Pourmand , "A molecular inversion probe (Figure 1A)

consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

13. Claims 68-70, 74-75, 79-82 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 13/266,862 in view of Pourmand (BMC informatics (2006) volume 7:500, pages 1-10). This is a provisional nonstatutory double patenting rejection.

Claim 1 of ‘862 is drawn to A method for analyzing a target nucleic acid, the method comprising:providing a sample comprising a target nucleic acid;contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes, each different molecular inversion probe comprising:a 5' region comprising a 5' terminal nucleotide;a 3' region comprising a 3' terminal nucleotide; anda central region flanked by the 5' region and the 3' region;wherein the 5' region ~~is~~ is complementary to anucleic acid residueflanking ~~the~~ a 3' end of one of a plurality of subregions of the target nucleic acid and the 3' region is complementary to a nucleic acid residue flanking a 5' end of the subregion;wherein each subregion is different and overlaps with at least one other subregion; andwherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence;wherein when hybridized to the target nucleic acid in a circular configuration, the 5' terminal nucleotide and the 3' terminal nucleotide of each probe are separated by a plurality of nucleotides on the target nucleic acid; converting hybridized probes into closed circularized probes;isolating a plurality of circularized probes having nucleic acid sequences of different subregions; and analyzing the isolated subregions.

Claim 13 of ‘862 teach, “wherein the obtaining comprises capturing target nucleic acids from a genomic sample of the subject with molecular inversion probes, each comprising a unique differentiator tag sequence.”

Claims of ‘862 do not specifically teach amplifying.

However, Pourmand teaches

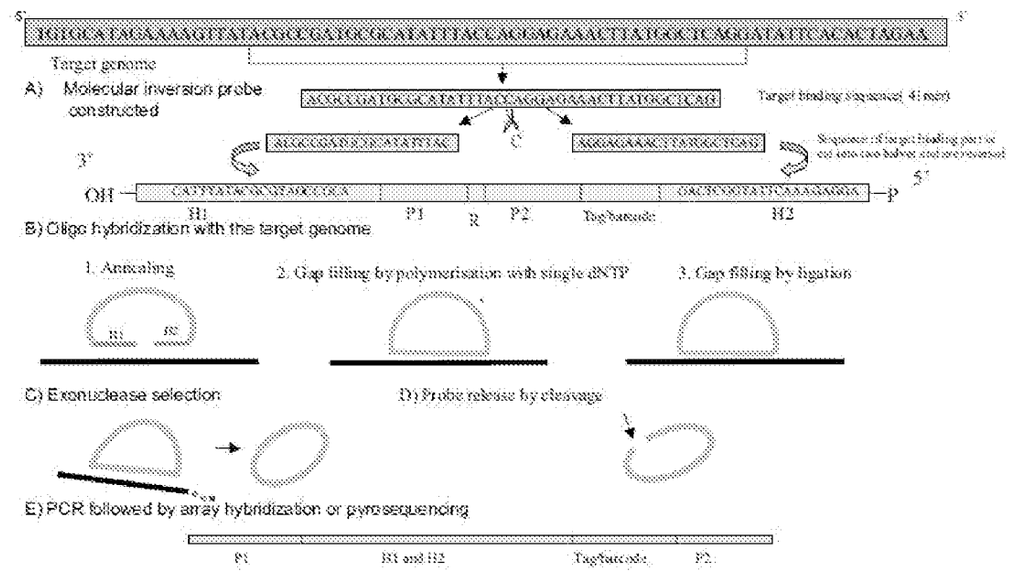

Figure 1

Poumard teaches, “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, “We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60℃, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, “MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.”(page 2, column 1, 1st full paragraph).

Other dependent claims are obvious variants of the methods of Pourmand and ‘862.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to improve the molecular inversion probe method of '862 with unique differentiator tags with amplifying and sequencing of Poumard. The artisan would be motivated to amplify and sequence the molecular inversion probes to increase the amount of nucleic acid being detected and thus increase the sensitivity by an art . The artisan would have a reasonable expectation of success as the artisan is merely be using art accepted methods of analysis of nucleic acid sequences using molecular inversion probes.

Response to Arguments

The response request the ODP rejection be held in abeyance. Thus the rejection is maintained.

Summary

No claims are allowed.

Akhras (PLOS one (2007) volume 2, e2230) is a reference that may be of interest.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN POHNERT, Ph.D. whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:00-5:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/STEVEN POHNERT/
Primary Examiner, Art Unit 1634

Notice of References Cited	Application/Control No. 15/231,687	Applicant(s)/Patent Under Reexamination PORRECA ET AL.	
	Examiner STEVEN POHNERT, Ph.D.	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A	US-				
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Akhras (PLOS one (2007) volume 2, e2230
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Petitioner Illumina, Inc., EX1003, p. 540

Electronic Acknowledgement Receipt	
EFS ID:	32466377
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Casey Suda
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	27-APR-2018
Filing Date:	08-AUG-2016
Time Stamp:	17:01:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1350
RAM confirmation Number	043018INTEFSW00005295500369
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		GSGE-002-04US-Response-to-FOA.pdf	29557 df1cbecf1f802f142eeef3fac44c67292d7f57de	yes	8

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of CPA/RCE	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	8

Warnings:

Information:

2	Request for Continued Examination (RCE)	GSGE-002-04US-RCE.pdf	1350008 cbc0da776698e4ac68dc0760a972321de728b42f	no	3

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	32424 c11af44014a20da7d38454a2e8921326937cdcab	no	2

Warnings:

Information:

Total Files Size (in bytes):	1411989

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE

This paper is in response to a final office action mailed October 27, 2017, from the United States Patent and Trademark Office. Applicant submits herewith a Request for Continued Examination (RCE) and pays the RCE fee. Applicant pays herewith the three-month extension of time fee, to bring the response deadline up to and including April 27, 2018.

Applicant believes no other fee is due with this paper. Nevertheless, Applicants authorize any and all required fees due with this response to be charged to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 5.

Amendments to the claims

Please amend the claims as follows. The following listing of claims will replace all prior versions of claims in the application.

1-67. (Canceled)

68. (Currently Amended) A method for nucleic acid identification, the method comprising the steps of:

applying a unique differentiator tag to each member of a plurality of target nucleic acid molecules obtained from a biological sample to generate a plurality of uniquely tagged target nucleic acid molecules~~, wherein each unique differentiator tag is distinct from any other unique differentiator tag~~;

amplifying said uniquely tagged target nucleic acid molecules to generate amplicons;

sequencing the amplicons obtained in said amplifying step; and

identifying a sequence for said nucleic acid molecules.

69. (Previously Presented) The method of claim 68, wherein said identifying step comprises identifying said unique differentiator tags.

70. (Previously Presented) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon the number of said unique differentiator tags.

71. (Withdrawn) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

Petitioner Illumina, Inc., EX1003, p. 545

72. (Withdrawn) The method of claim 71, wherein said common identifier is used to identify a sample source.

73. (Withdrawn) The method of claim 72, wherein said common identifier is used to identify a patient.

74. (Previously Presented) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (Previously Presented) The method of claim 68, wherein said plurality of nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (Withdrawn) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

77. (Withdrawn) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

78. (Withdrawn) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

79. (Canceled)

80. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are circulating tumor nucleic acid molecules.

81. (Previously Presented) The method of claim 68, further comprising the step of determining the copy number of a genomic region or transcript in a patient from whom the sample is obtained.

82. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are maternally-circulating fetal or placental nucleic acid molecules.

Petitioner Illumina, Inc., EX1003, p. 547

Remarks

Claims 68-70, 74, 75, and 80-82 are pending in the application. Claim 68 is amended and claim 79 is canceled. Support for the amendment is found throughout the as-filed application, including at page 42. No new matter is added.

Rejections under 35 U.S.C. §112

The office action rejects claims 68-70, 74, 75, and 79-82 under 35 U.S.C. §112 as being indefinite for reciting wherein each unique differentiator tag is distinct from any other unique differentiator tag. Claim 68 is amended to recite that unique differentiator tags are applied to target nucleic acid molecules to generate a plurality of uniquely tagged target nucleic acid molecules. Support for the products having unique target-differentiator tag sequences is found on page 42 of the application as-filed, as the office action points out on page 4.

Applicant submits that the §112 rejection is overcome and should be withdrawn.

Rejections under 35 U.S.C. §102

The office action states that claims 68, 69, 74, 75, and 81 are rejected under 35 U.S.C. §102(b) over Pourmand (BMC Informatics, 2006, 7:500). Applicant disagrees.

In order to anticipate a claim, the Patent Office requires that a single prior art reference teach each and every element of the claim. MPEP §2131. Pourmand fails to show applying a distinct and unique differentiator tag to each member of a plurality of nucleic acid molecules to generate a plurality of uniquely tagged target nucleic acid molecules.

The claimed method uses tags to uniquely identify individual molecules and follow them through the amplification reaction. The method therefore allows the starting molecules to be distinguished from each other, to overcome bias associated with systematic and random errors in genome capture, amplification, and sequencing. *See application as-filed, page 8.* While the present claims require uniquely tagging each molecule to generate uniquely tagged target nucleic

acid molecules, Pourmand only discloses comparing one group of like-sequences to another, but not for distinguishing from among like-sequences to discern the particular molecule of origin. Unlike Pourmand, the present invention allows a sequence to be traced back to a particular starting molecule.

Pourmand merely shows methods for designing barcoded molecular inversion probes (MIPs) that can detect SNPs, as was commonplace prior to the present disclosure. *See Pourmand, page 4, first column, last paragraph, through second column, first paragraph.* The barcodes can distinguish SNPs from each other, but are not designed to differentiate the particular starting molecule from all other molecules. The MIPs are merely designed with a "molecular barcode for each genotype" *Id., page 2, left column.* Pourmand simply applies tags, amplifies, and then observes the relative numbers of one SNP versus another. Unlike the claimed methods, Pourmand's method of ensemble averaging does not distinguish one starting molecule from another, and therefore cannot accomplish the goal of minimizing bias. Pourmand's method merely allows groups of molecules—not individual molecules—to be distinguished.

Since the presently amended claims recite applying a unique differentiator tag to each member of a plurality of target nucleic acid molecules to generate uniquely tagged target nucleic acid molecules, which Pourmand does not disclose or suggest, Applicant submits that Pourmand does not anticipate the claims. Accordingly, the §102 rejection is overcome.

Rejections under 35 U.S.C. §103

The office action states that claims 68-70, 74, 75, 79, and 81 are rejected under 35 U.S.C. §103 over Pourmand in view of Meyer (Nat. Prot., 2008, 3:267-78). The office action states that claims 68-69, 74, 75, and 81 are rejected under 35 U.S.C. §103 over Pourmand in view of Shoemaker (US 2008/0090239). Applicant submits that the claims are not obvious over any combination of those references.

In order to establish a prima facie case of obviousness, the prior art must provide motivation to modify a reference or to combine multiple references in a manner that would lead one of ordinary skill in the art to an applicant's claimed invention with a reasonable expectation of success. *See e.g., KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); and MPEP § 2143. Furthermore, an obviousness rejection cannot be established unless each claim element is disclosed in the cited art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Without a reference disclosing the missing claim elements, there can be no motivation of achieving the claimed invention or likelihood of success in doing so. *See Wyers v. Master Lock Co.*, 616 F.3d 1231 (Fed. Cir. 2010) (providing a prima face case requires a teaching or suggestion of all claim limitations along with an apparent reason to combine the references).

As discussed in the section above, Pourmand fails to disclose each and every claim element. Meyer and Shoemaker do not make up for what Pourmand lacks. Meyer merely reports a molecular barcoding method for sequencing multiple samples on the 454 platform. *See Meyer, Abstract.* But Meyer does not disclose using MIPs to generate uniquely tagged target nucleic acid molecules. Shoemaker reports the use of nucleic acids from circulating tumor samples and fetal samples. *Shoemaker, paragraph [0004].* Shoemaker does not disclose or suggest applying a unique differentiator tag to each target nucleic acid to generate uniquely tagged molecules that can be used to identify amplicons. As with Pourmand, neither Meyer nor Shoemaker discloses the element of applying a unique differentiator tag to each nucleic acid molecule to generate a plurality of uniquely tagged target nucleic acid molecules. Accordingly, no combination of those references makes the present claims obvious.

Applicant submits that the §103 rejection is overcome and should be withdrawn.

Double Patenting

Claims 68-70, 74, 75, and 79-82 are provisionally rejected on the ground of nonstatutory double patenting over claim 1 of copending application no. 13/266,862 in view of Pourmand. Since the rejection is provisional, Applicant requests that it be held in abeyance.

Summary

If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative.

Dated: April 27, 2018

Respectfully submitted,
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63015341 v1

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	15/231,687	Filing Date	2016-08-08	Docket Number (if applicable)	GSGE-002/04US 29258/78	Art Unit	1634
First Named Inventor	Gregory Porreca			Examiner Name	POHNERT, STEVEN C		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 500369

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

EFS - Web 2.1.16

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2018-04-27
Name	Thomas C. Meyers	Registration Number	36989

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal	
Application Number:	15231687
Filing Date:	08-Aug-2016
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78
Filed as Small Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	700	700
Miscellaneous:				
RCE- 1ST REQUEST	2801	1	650	650
		Total in USD ($)		**1350**

Electronic Acknowledgement Receipt

EFS ID:	32467111
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Casey Suda
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	27-APR-2018
Filing Date:	08-AUG-2016
Time Stamp:	19:00:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	WO2014074246A1.pdf	4504744 3375f3c445037f3ff62bc6aa2aca0c442de66d33	no	74

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Information:					
2	Foreign Reference	WO2004018497.pdf	4640674 8cc191778df049047076aaa5ee4c6ad9554134a5	no	134
Warnings:					
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3	Foreign Reference	WO2005003304.pdf	8811059 a978816da74d7dc1d7bd3c8af0cd0b45d3e08e81	no	156
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4	Foreign Reference	WO2013191775A2.pdf	6434915 c259c1ed75328c02bf8d1c8bf394084fe7297ce3	no	106
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5	Foreign Reference	WO2008067551A2.pdf	10158485 ebd1e895348efa410459ff28d008e52852ae9bd5	no	184
Warnings:					
Information:					
6	Foreign Reference	Examination_Report_for_EP_10770071-8.pdf	130738 8cf5c9d1bbf94c3c29ed8e956e9f21a004c9e434	no	5
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7	Non Patent Literature	Adey.pdf	3838754 7ea8bd8b8e62349ca0d11c89c0fc549889c6ae05	no	17
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Information:					
8	Non Patent Literature	Agrawal-1990-Tetrahedronletters_11.pdf	505012 53582280f0e206336364748c66759db511acf486	no	4
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9	Non Patent Literature	Archer-2014-BMCGenomics.pdf	691341 b3ba450bc9e88059438ed585d4b0930c020fef02	no	9
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10	Non Patent Literature	Balzer-2013-Bioinformatics.pdf	495201 26bbd2d8412bb6f8216f1d8bd14d1512dc21bbf5	no	7
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11	Non Patent Literature	Bell-2011-SciTransMed.pdf	4318920 f24b1a3312aa9b6cea6a2e03eef762de55804711	no	15
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12	Non Patent Literature	Bonfield-2013-PLoSOne.pdf	1295556 4b0360604406c103da9f3205fd6a731c17460266	no	10
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13	Non Patent Literature	Bose-2012-JBiosci.pdf	134095 4570082731e37e17cd0ea225beb7f7aedd14a4dc	no	5
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14	Non Patent Literature	Boyden-2013-ASHGmtg.pdf	151171 24024cac7294653c1e47abfc283680bf10df5ce8	no	2
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15	Non Patent Literature	Brinkman.pdf	1202568 90a57fba60a0ae15c8abec3cb65f1f9b8dfbbad6	no	11
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16	Non Patent Literature	Brownstein-2014-GenomeBiol.pdf	1004460 2df719ef3e2df52b6f4dd8c46605c9254b51747d	no	18
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17	Non Patent Literature	Carpenter-2013-AmJHumGenet.pdf	1449677 307d4a69125fb4eb5b2ee8843eb8d4f5cb4bab88	no	13
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18	Non Patent Literature	29168_244US_-_Caruthers-1985-Science.pdf	1255720 5d31314ae5938580e05885ec5277c02c2f062883	no	5
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19	Non Patent Literature	Challis-2012-BMC.pdf	2746002 c41f5ec6129009d4ffebdf203f905cedbcea9c64	no	12
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20	Non Patent Literature	Chen-2010-Genetics.pdf	1906842 526a17e50a4e05323a65d2aecf95b75b73cd75fc	no	10
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21	Non Patent Literature	Chennagiri-2013-ASHGmtg.pdf	156838 5f25b7a42361a22f3197ffe8c3744c47c38d9f22	no	2
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22	Non Patent Literature	Cock-2010-NucAcRes.pdf	198289 c3aa9cadf34cb361b5617766f3bc73b2706cdedb	no	5
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24	Non Patent Literature	Cronin.pdf	1307789 0c3a11eb3009387f660adac8f5107aa876373b45	no	12
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25	Non Patent Literature	Danecek-2011-Bionformatics.pdf	273118 a894d61ce58f1cdf793353345dcb93c2b9f9a647	no	3
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26	Non Patent Literature	denDunnen-2003-CPHG.pdf	137246 295e910312faf51c9257ecae396dbc33b9f60778	no	8
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27	Non Patent Literature	Deorowicz-2013-AlgforMoleBio.pdf	1154597 3acac44fbad73f90ee5d17e3e87bccf480c56a16	no	13
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30	Non Patent Literature	Faust-2014-Bionformatics-Online.pdf	212504 e72b0c825df9d07ab9a8104a0e4d8abb5d03457b	no	2
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31	Non Patent Literature	Fitch-1970-SystBiol.pdf	4058315 80eee3402eee64bac924a270c962defdbbb601fc	no	15
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32	Non Patent Literature	Furtado-2011-BMCMedGen.pdf	1227309 398ce8c139ddbde7992e6a38bec1bfeefb37c9f4	no	7
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33	Non Patent Literature	Garber-2008-NatBiotech.pdf	162718 55720bc5156d04e7a48b5fe110b27c0b90d1f2bc	no	4
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34	Non Patent Literature	Garber-2008-NatBiotech2.pdf	183172 533c8c7af4bdc4d1c54df524fe49743b9368b121	no	4
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36	Non Patent Literature	Goto-1994-Kyushu.pdf	2500624 ad90cce8e72fc072adc653db9a669e78dd19077e	no	106
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37	Non Patent Literature	Green-2005-ApplEnvMicrob.pdf	154858 71470bdaf310c4356d14a3014baa1185e276ebcf	no	7
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38	Non Patent Literature	Guerrero-Fernandez-2013-Granada.pdf	406234 16b9f3afa920527b86036e6ce34af8bc21e04cea	no	8
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39	Non Patent Literature	Gupta-1991-NuclAcRec.pdf	787127 76780da2dee86b1559270755076b5eff985c2981	no	7
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40	Non Patent Literature	Gustincich-Biotechniques-1991.pdf	1830923 8c5c119be0616a6c03f74095dd8191ab6837b04d	no	4
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41	Non Patent Literature	Hallam-2014-JMolDiag.pdf	15010588 21e01da7c74d48247762c05bb52bef29b797324b	no	10
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42	Non Patent Literature	Hardenbol-2005-GenomeRes.pdf	278386 91cb79b7245ad59c42013636041d3502904c088c	no	7
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49	Information Disclosure Statement (IDS) Form (SB08)	IDS_1.pdf	1041304 78b1d3b01fa25a58a62e58d6a5942de0dfa30a7d	no	18
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50	Non Patent Literature	Meyer_2007_NAR.pdf	1154866 36c47fdd6ea4a03ee2bba690733b57ba3b56d0b8	no	5
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Information:					

51	Non Patent Literature	isr_pctus2016013346.pdf	1255588 f9e00894509f80b3d656b61a415940d98e8cb7ec	no	7
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52	Non Patent Literature	ISRWO_PCTUS2015056037.pdf	1774702 834b5eade9f027a15942b915ceb44425704c7580	no	13
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53	Non Patent Literature	Smith_2010_NAR.pdf	273392 6d2aa8a556614edb73fe1091210d0cf8df474992	no	7
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54	Non Patent Literature	HarrisScience2008.pdf	491853 b92252356a84758d8f8755c4d86815dcf9ecd38f	no	4
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2018-04-27
Name/Print	Thomas C. Meyers	Registration Number	36,989

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5060980		1991-10-29	Johnson et al.	
	2	5210015		1993-05-11	Gelfand et al.	
	3	5348853		1994-09-20	Wang et al.	
	4	5459307		1995-10-17	Klotz, Jr.	
	5	5486686		1996-01-23	Zdybel, Jr. et al.	
	6	5567583		1996-10-22	Wang et al.	
	7	5869717		1999-02-09	Frame et al.	
	8	5888788		1999-03-30	De Miniac	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

	9	5942391		1999-08-24	Zhang et al.	
	10	5971921		1999-10-26	Timbel	
	11	5994056		1999-11-30	Higuchi	
	12	6033854		2000-03-07	Kumit et al.	
	13	6033872		2000-03-07	Bergsma et al.	
	14	6171785		2001-01-09	Higuchi	
	15	6197574		2001-03-06	Miyamoto et al.	
	16	6235502		2001-05-22	Weissman et al.	
	17	6360235		2002-03-19	Tilt et al.	
	18	6462254		2002-10-08	Vernachio et al.	
	19	6569920		2003-05-27	Wen et al.	

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	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

	20	6585938		2003-07-01	Machida et al.	
	21	6613516		2003-09-02	Christians et al.	
	22	6716580		2004-04-06	Gold et al.	
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	24	6941317		2005-09-06	Chamberlin et al.	
	25	7074586		2006-07-11	Cheronis et al.	
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	28	7629151		2009-12-08	Gold et al.	
	29	7642056		2010-01-05	Ahn et al.	
	30	7774962		2010-08-17	Ladd	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

	31	7985716		2011-07-26	Yershov et al.	
	32	8283116		2012-10-09	Bhattacharyya et al.	
	33	8462161		2013-06-11	Barber	
	34	8463895		2013-06-11	Arora et al.	
	35	8474228		2013-07-02	Adair et al.	
	36	8496166		2013-07-30	Burns et al.	
	37	8529744		2013-09-10	Marziali et al.	
	38	8778609		2014-07-15	Umbarger	
	39	8812422		2014-08-19	Nizzari et al.	
	40	8847799		2014-09-30	Kennedy et al.	
	41	8976049		2015-03-10	Kennedy et al.	

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	Application Number	15231687
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	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

	42	9074244		2015-07-07	Sparks et al.	
	43	9228233		2016-01-05	Kennedy et al.	
	44	9292527		2016-03-22	Kennedy et al.	
	45	9535920		2017-01-03	Kennedy et al.	
	46	9567639		2017-02-14	Oliphant et al.	

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	1	20020040216	A1	2002-04-04	Dumont et al.	
	2	20020091666	A1	2002-07-11	Rice et al.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
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	Attorney Docket Number	GSGE-002/04US 29258/78

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	6	10770071.8	EP		2010-11-04	Good Start Genetics, Inc.		

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	50	International Search Report and Written Opinion for PCT/US2013/036575 dated August 12, 2013, 10 pages.	

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PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	23 December 2015 (23.12.2015)
Applicant's or agent's file reference GSGE-029/01WO 29258/146	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/US2015/056037**	International filing date *(day/month/year)* **16 October 2015 (16.10.2015)**

Applicant
GOOD START GENETICS, INC.

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 . 9-011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months** from the priority date, the applicant may request that a supplementary international search be carried out by an International Searching Authority, that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/KR International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea	Authorized officer COMMISSIONER
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Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for six months(expire date : **2016.06.23**) from the date of mailing of the international search report.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-029/01WO 29258/146	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2015/056037**	International filing date *(day/month/year)* **16 October 2015 (16.10.2015)**	(Earliest) Priority Date *(day/month/year)* 17 October 2014 (17.10.2014)
Applicant **GOOD START GENETICS, INC.**		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **4** sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
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6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
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   b. ☒ none of the figures is to be published with the abstract.

Petitioner Illumina, Inc., EX1003, p. 587

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/056037

A. CLASSIFICATION OF SUBJECT MATTER

C12Q 1/68(2006.01)i, G06F 19/20(2011.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q 1/68; C40B 20/00; C40B 40/06; G06F 19/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: pre-implantation genetic screening, aneuploidy detection, embryo, Z-score

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014-0206552 A1 (NATERA, INC.) 24 July 2014 See abstract; claims 1-7; paragraphs [0002]-[0045], [0128]-[0171], [0222]-[0234].	1-26
A	US 2012-0270212 A1 (RABINOWITZ et al.) 25 October 2012 See abstract; claims 1-43; and paragraph [0426].	1-26
A	US 2013-0288242 A1 (STOUGHTON et al.) 31 October 2013 See the whole document.	1-26
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☐ Further documents are listed in the continuation of Box C.

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23 December 2015 (23.12.2015)	**23 December 2015 (23.12.2015)**

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PCT/US2015/056037

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014-0206552 A1	24/07/2014	None	
US 2012-0270212 A1	25/10/2012	AU 2011-358564 A1	05/09/2013
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		EP 2885445 A1	24/06/2015
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		WO 2014-018080 A1	30/01/2014

Petitioner Illumina, Inc., EX1003, p. 589

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/056037

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2014-028778 A1	20/02/2014
US 2013-0288242 A1	31/10/2013	US 2008-0050739 A1	28/02/2008
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		US 2013-0280709 A1	24/10/2013
US 2008-0085836 A1	10/04/2008	None	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**23 December 2015 (23.12.2015)**
Applicant's or agent's file reference GSGE-029/01WO 29258/146	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2015/056037	**16 October 2015 (16.10.2015)**	17 October 2014 (17.10.2014)

International Patent Classification (IPC) or both national classification and IPC

C12Q 1/68(2006.01)i, G06F 19/20(2011.01)i

Applicant

GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea Facsimile No. +82-42-472-7140	23 December 2015 (23.12.2015)	KIM, Seung Beom Telephone No. +82-42-481-3371

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/056037

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:
      ☐ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/056037

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	12-13,26	YES
	Claims	1-11,14-25	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-26	NO
Industrial applicability (IA)	Claims	1-26	YES
	Claims	NONE	NO

2. Citations and explanations :

※ NOTE: The written opinion has been established as if claim 26 had referred to claim 18 instead of claim 1.

Reference is made to the following document:
D1: US 2014-0206552 A1 (NATERA, INC.) 24 July 2014

1. Novelty and Inventive Step

1.1. Claims 1-17

1.1.1. Independent Claim 1

Claim 1 relates to a method for determining ploidy of an embryo, the method comprising:
(a) amplifying, using a primer pair that amplifies a plurality of human genomic loci, nucleic acid from a preimplantation embryo to generate a plurality of amplicons;
(b) sequencing the amplicons to generate a plurality of sequence reads;
(c) matching the sequence reads to the genomic loci and counting a number of matches; and
(d) determining chromosome count based on the number of matches.

D1, which is considered to be the closest prior art to the subject matter of claim 1, discloses a method for determining a ploidy state of an embryo at a chromosome of interest, the method comprising:
(a') obtaining a genetic sample from the embryo and preparing the genetic sample for sequencing, wherein the preparing step comprises preferentially enriching the DNA in the genetic sample at a plurality of polymorphic loci by performing targeted PCR amplification of the DNA;

Continued on Supplemental Box

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/056037

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 relates to a method, but claim 26 dependent on claim 1 relates to a system. As claim 26 does not clearly define the matter for which protection is sought, this claim does not meet the requirement of PCT Article 6.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Box No. V

(b') sequencing the genetic sample to give sequencing data;
(c') counting the number of sequence reads in the sequence data associated with each of the plurality of loci on the chromosome of interest; and
(d') determining the most likely ploidy state of the chromosome of interest given the sequence read count associated with each allele (see claims 1, 6-7).

D1 also discloses that in the targeted PCR, forward and reverse primers anneal the same fragment to enable amplification, and the method of D1 is used for preimplantation genetic diagnosis (see paragraphs [0002], [0151]). Accordingly, claim 1 is substantially the same as D1.

Therefore, claim 1 lacks novelty under PCT Article 33(2) and does not involve an inventive step under PCT Article 33(3).

1.1.2. Dependent Claims 2-11, 14-17

Concerning the additional features of claims 2-7, D1 discloses the step of obtaining the genetic sample from the embryo, wherein the genetic sample is one to five cells biopsied from the embryo, and also discloses a trophectoderm biopsy (see claims 1-2; and paragraph [0230]).

Concerning the additional features of claims 8-11, D1 discloses a multiplex pool of PCR assays designed to amplify SNP loci on chromosomes X, Y, 13, 18 and 21 (see paragraph [0171]). D1 also discloses that targeted PCR targets a plurality of loci on the chromosome of interest and on one or more reference chromosomes, wherein the reference chromosomes are assumed to be disomic (see paragraphs [0022], [0045]).

Concerning the additional features of claims 14-16, D1 discloses that sequencing adapters with barcodes are added to the PCR products, and that a second round of PCR is used to amplify the sequences with universal primer sequences (see paragraphs [0148], [0234]).

Concerning the additional feature of claim 17, D1 discloses that the DNA is highly fragmented (see paragraph [0151]).

Consequently, claims 2-11 and 14-17 lack novelty under PCT Article 33(2) and do not involve an inventive step under PCT Article 33(3).

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Supplemental Box

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1.1.3. Dependent Claims 12-13

The additional feature of claim 12 defines the determining step as comprising the generation and comparison of a z-score for a chromosome of interest, rendering this claim different from D1. However, the z-score in chromosome count can be easily derived by a person skilled in the art within technical common sense.

The additional feature of claim 13 further comprises determining a euploidy or aneuploidy state of the embryo based on the chromosome count, rendering this claim different from D1. However, D1 discloses that the method of D1 can detect possible ploidy states comprising aneuploidy and euploidy (see abstract; and paragraph [0222]). Accordingly, claim 13 would have been obvious in view of D1.

Consequently, claims 12-13 are considered to be novel under PCT Article 33(2), but do not involve an inventive step under PCT Article 33(3).

1.2. Claims 18-26

1.2.1. Independent Claim 18

Claim 18 relates to a system for determining chromosome count, the system comprising a processor coupled to a tangible memory subsystem storing instructions that when executed by the processor cause the system to:
(a) obtain sequence reads from amplicons, wherein the amplicons are generated by amplifying, using a primer pair that amplifies a plurality of human genomic loci, nucleic acid from a preimplantation embryo;
(b) match the sequence reads to the genomic loci;
(c) count a number of matches at the genomic loci; and
(d) determine chromosome count based on the number of matches.

As described in point 1.1, D1 discloses the method for determining a ploidy state of the embryo comprising steps corresponding to the steps (a)-(d) of claim 18. D1 also discloses a computer program product tangibly embodied in a machine-readable storage device for execution by a programmable processor, and method steps of D1 can be performed by the programmable processor executing a program of instructions to perform functions by operating on input data and generating output (see paragraph [0128]). Accordingly, claim 18 is

Continued on The Next Page

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Previous Page

substantially the same as D1.

Therefore, claim 18 lacks novelty under PCT Article 33(2) and does not involve an inventive step under PCT Article 33(3).

1.2.2. Dependent Claims 19-25

The additional features of claims 19-25 correspond to the features of claims 2-4, 7-8 and 10-11, respectively. Accordingly, as reviewed under points 1.1.2 and 1.2.1, claims 19-25 are substantially the same as D1.

Consequently, claims 19-25 lack novelty under PCT Article 33(2) and do not involve an inventive step under PCT Article 33(3).

1.2.3. Dependent Claim 26

The additional feature of claim 26 defines the instructions as causing the system to determine and report a euploidy or aneuploidy state of the embryo based on the chromosome count, rendering this claim different from D1.

However, as described in point 1.1.3, D1 discloses that the method of D1 can detect possible ploidy states comprising aneuploidy and euploidy. Accordingly, claim 26 would have been obvious in view of D1.

Therefore, claim 26 is considered to be novel under PCT Article 33(2), but does not involve an inventive step under PCT Article 33(3).

2. Industrial Applicability

Claims 1-26 are industrially applicable under PCT Article 33(4).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

ENTERED IN CPI

PCT

To: Thomas C. Meyers
Brown Rudnick LLP
One Financial Center
Boston, MA 02111
United States of America

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference GSGE-014/01 WO 29258/64	Date of mailing *(day/month/year)* **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US13/62842	International filing date *(day/month/year)* 01 October 2013 (01.10.2013)
Applicant Good Start Genetics, Inc.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46).

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774 Telephone No.

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: Thomas C. Meyers
Brown Rudnick LLP
One Financial Center
Boston, MA 02111
United States of America

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference GSGE-014/01 WO 29258/64	Date of mailing *(day/month/year)* 04 FEB 2014 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US13/62842	International filing date *(day/month/year)* 01 October 2013 (01.10.2013)
Applicant Good Start Genetics, Inc.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-014/01 WO 29258/64	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US13/62842	International filing date *(day/month/year)* 01 October 2013 (01.10.2013)	(Earliest) Priority Date *(day/month/year)* 07 November 2012 (07.11.2012)
Applicant Good Start Genetics, Inc.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 1

   ☐ as suggested by the applicant.

   ☒ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/62842

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/62842

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G06N 3/12, 7/02; G06F 17/10 (2013.01)
USPC - 706/13, 21; 702/19
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): G06N 3/12, 7/02; G06F 3/00, 17/00, 17/10, 15/18; A61B 5/00, 5/07; C40B 40/10, 40/00, 60/10; A61N 1/30; C12Q 1/68 (2013.01)
USPC Classification(s): 706/13, 21, 52, 15; 702/19; 703/1; 424/422; 600/300, 483; 506/13, 18, 38, 7; 250/282

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google/Google Scholar; ScienceDirect; ProQuest; Search Terms: genetic, mutation, test, evaluate, computer, sequence, pipeline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LI, M et al. A New Approach for Detecting Low-level Mutations in Next-generation Seqence Data. Genome Biology. 23 May 2012, Vol. 13, pp. 1-15; page 4, left column, second paragraph; page 12 right column, second paragraph. DOI: 10.1186/gb-2012-13-5-r34	1-11
Y	US 2012/0252684 A1 (SELIFONOV, S et al.) October 4, 2012; abstract; paragraphs [0027], [0080], [0138], [0139], [0147].	1-11
Y	US 8209130 B1 (KENNEDY, C et al.) June 26, 2012; abstract; column 2, lines 20-21; column 2, lines 44-45; column 3, lines 18-24; column 3, lines 63-64; column 4, lines 1-5; column 5, lines 48-52	6-8, 10, 11
Y	EP 1321477 B1 (GRAWUNDER, U et al.) October 13, 2004; page 5, lines 24-27; page 17, lines 32-33	4

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 December 2013 (30.12.2013)	04 FEB 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Thomas C. Meyers
Brown Rudnick LLP
One Financial Center
Boston, MA 02111
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	04 FEB 2014
Applicant's or agent's file reference GSGE-014/01 WO 29258/64	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US13/62842	01 October 2013 (01.10.2013)	07 November 2012 (07.11.2012)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G06N 3/12, 7/02; G06F 17/10 (2013.01)
USPC - 706/13, 21; 702/19

Applicant Good Start Genetics, Inc.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to th IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	30 December 2013 (30.12.2013)	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US13/62842

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US13/62842

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-11	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-11	NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3, 5, and 9 lack an inventive step under PCT Article 33(3) as being obvious over the article entitled 'A new approach for detecting low-level mutations in next-generation sequence data' by Li, et al. (hereinafter 'Li') in view of US 2012/0252684 A1 to Selifonov, et al. (hereinafter 'Selifonov').

As per claim 1, Li discloses a method of evaluating a genetic test (we developed a new method that distinguishes real mutations (genetic test) from sequencing errors and test it using three different distributions to evaluate the performance of our method compared to two others; page 4, left column, second paragraph), the method comprising: obtaining, using a computer (here we provided a novel computation method (on a computer system), all common variation positions were flagged in the output file; page 12, right column, second paragraph; supplemental page 5, second paragraph), a plurality of sequence reads (for each bin at a specific position we counted the number of reads with major and minor alleles for the individual (individual sequence) in question as well as the same numbers for the reference individuals (plurality of sequences); supplemental page 3, second paragraph); analyzing the sequence reads using a genetic pipeline (all samples (sequence reads) are analyzed following the same pipeline; page 11, left column, second paragraph); determining if the genetic pipeline identified the mutation (figure 4 shows the low level mutations and sequencing errors detected by the genetic pipeline; page 5, figure 4), thereby validating the genetic pipeline (our method (genetic pipeline) showed a better performance because the empirical error rate is low, making it easier to distinguish real low-level mutations from sequencing errors (simulated mutations); page 8, right column, third paragraph). Li does not disclose a computer comprising a non-transitory memory; introducing, using the computer, a simulated mutation into at least one of the plurality of sequence reads. Selifonov discloses a computer comprising a non-transitory memory (the data structure is designed for a computer can be formed in computer memory such read-only memory (non-transitory memory); paragraph [0147]); introducing, using the computer (the computer program comprises computer code that performs the operations described herein; paragraph [0020]), a simulated mutation into at least one of the plurality of sequence reads (the methods of this invention can be used to introduce variation into the initial strings (plurality of sequence reads) the mutations can be random or can be placed into a specific subunit; paragraphs [0027], [0138], [0139]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the computer induced mutations, as previously disclosed by Selifonov, as the previous disclosure by Li includes the use of known mutations to test and verify next generation sequencing technologies in order to improve discovery of genetic variation in populations, Selifonov discloses a method for increasing genetic variation in a population by introducing simulated mutations (Selifonov; abstract), and a combination of these references would have resulted in a superior method of evaluating a genetic test.

As per claim 2, Li and Selifonov, in combination, disclose the method of claim 1, and Li further discloses introducing artificial DNA into about half of the plurality of sequence reads (artificially mixing of 2 DNA samples was done at a ratio of 1:1; page 13, left column, second paragraph). Li does not disclose introducing the simulation sequence. Selifonov discloses introducing the simulation sequence (the methods of this invention can be used to introduce variation into the initial strings (plurality of sequence reads) the mutations can be random or can be placed into a specific subunit; paragraphs [0027], [0138], [0139]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the computer induced mutations, as previously disclosed by Selifonov, as the previous disclosure by Li includes the use of known mutations to test and verify next generation sequencing technologies in order to improve discovery of genetic variation in populations, Selifonov discloses a method for increasing genetic variation in a population by introducing simulated mutations (Selifonov; abstract), and a combination of these references would have resulted in a superior method of evaluating a genetic test.

As per claim 3, Li and Selifonov, in combination, disclose the method of claim 1, but Li does not disclose wherein introducing the simulated mutation comprises manipulating a data field for base sequence or quality. Selifonov discloses wherein introducing the simulated mutation comprises manipulating a data field for base sequence (the methods of this invention can be used to introduce variation into the initial strings (plurality of sequence reads) the mutations can be random or can be placed into a specific subunit, the data structure can be manipulated by an appropriate computer; paragraphs [0027], [0138], [0139], [0147]) or quality. It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the computer induced mutations, as previously disclosed by Selifonov, as the previous disclosure by Li includes the use of known mutations to test and verify next generation sequencing technologies in order to improve discovery of genetic variation in populations, Selifonov discloses a method for increasing genetic variation in a population by introducing simulated mutations (Selifonov; abstract), and a combination of these references would have resulted in a superior method of evaluating a genetic test.

-***-Continued Within the Next Supplemental Box-***-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US13/62842

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
-***-Continued from Box V: Citations and Explanations-***-

As per claim 5, Li and Selifonov, in combination, disclose the method of claim 1, and Li further discloses assembling the sequence reads (page 2, Figure 1). Li does not disclose the method comprising assembling the sequence reads prior to introducing the simulated mutation. Selifonov discloses the method comprising assembling the sequence reads prior to introducing the simulated mutation (the variation (mutation) can be introduced in to the concatenated string output (after assembling has occurred); paragraphs [0138], [0182], [0183]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the computer induced mutations, as previously disclosed by Selifonov, as the previous disclosure by Li includes the use of known mutations to test and verify next generation sequencing technologies in order to improve discovery of genetic variation in populations, Selifonov discloses a method for increasing genetic variation in a population by introducing simulated mutations (Selifonov; abstract), and a combination of these references would have resulted in a superior method of evaluating a genetic test.

As per claim 9, Li and Selifonov, in combination, disclose the method of claim 1, but Li does not disclose using the computer to automatically introduce a number of different simulated mutations into different ones of the plurality of sequence reads. Selifonov discloses using the computer (the computer program comprises computer code that performs the operations described herein; paragraph [0020]) to automatically introduce a number of different simulated mutations into different ones of the plurality of sequence reads (the methods of this invention can be used to introduce variation into the initial strings (plurality of sequence reads) automatically using a computer, the mutations can be random or can be placed into a specific subunit; paragraphs [0027], [0080], [0138], [0139]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the computer induced mutations, as previously disclosed by Selifonov, as the previous disclosure by Li includes the use of known mutations to test and verify next generation sequencing technologies in order to improve discovery of genetic variation in populations, Selifonov discloses a method for increasing genetic variation in a population by introducing simulated mutations (Selifonov; abstract), and a combination of these references would have resulted in a superior method of evaluating a genetic test.

Claims 6-8, 10, and 11 lack an inventive step under PCT Article 33(3) as being obvious over Li in view of Selifonov, in further view of US 8,209,130 B1 to Kennedy, et al. (hereinafter 'Kennedy').

As per claim 6, Li and Selifonov, in combination, disclose the method of claim 1, but Li does not disclose wherein the analyzing step comprises assembling the plurality of sequence reads to produce a contig. Kennedy discloses wherein the analyzing step comprises assembling the plurality of sequence reads to produce a contig (nucleic acid obtained from a subject is sequenced to produce a plurality of reads and the methods of the invention are accomplished by assembling contigs from sequence reads; column 2, lines 20-21; column 2, lines 44-45). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the assembly of sequence reads to produce contigs, as previously described by Kennedy, as the previous disclosure by Li includes identifying low-level mutations in sequences, and the Kennedy reference includes identifying mutations based on alignments to references (Kennedy; abstract), and the combination of these references would have resulted in the use of a superior method to evaluate a genetic test that would have produced a contig that could be compared to a reference sequence.

As per claim 7, Li, Selifonov, and Kennedy, in combination, disclose the method of claim 6, but Li does not disclose wherein the analyzing step further comprises aligning the contig to a reference. Kennedy discloses wherein the analyzing step further comprises aligning the contig to a reference (mutations are identified based on the alignments to the reference and to the contig; abstract). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the assembly of sequence reads to produce contigs, as previously described by Kennedy, as the previous disclosure by Li includes identifying low-level mutations in sequences, and the Kennedy reference includes identifying mutations based on alignments to references (Kennedy; abstract), and the combination of these references would have resulted in the use of a superior method to evaluate a genetic test that would have produced a contig that could be compared to a reference sequence.

As per claim 8, Li, Selifonov, and Kennedy, in combination, disclose the method of claim 7, but Li does not disclose wherein the analyzing step further comprises aligning one or more of the plurality of sequence reads to the contig. Kennedy discloses wherein the analyzing step further comprises aligning one or more of the plurality of sequence reads to the contig (with the contigs aligned, each raw read is aligned to a contig in a local alignment, all reads (plurality) can align as a perfect match; figures 1, 2; column 4, lines 1-2; column 4, lines 4-5). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the alignment method, as previously described by Kennedy, as the previous disclosure by Li includes identifying low-level mutations in sequences, and the Kennedy reference includes identifying mutations based on alignments to references (Kennedy; abstract), and the combination of these references would have resulted in the use of a superior method to evaluate a genetic test that would be capable of identifying mutations.

As per claim 10, Li and Selifonov, in combination, disclose the method of claim 1, and Li further discloses the genetic pipeline (our method (genetic pipeline) showed a better performance because the empirical error rate is low, making it easier to distinguish real low-level mutations from sequencing errors (simulated mutations); page 8, right column, third paragraph). Li does not disclose comprising instructions in the memory operable to cause the computer to assemble the plurality of sequence reads. Kennedy discloses instructions in the memory operable to cause the computer to assemble the plurality of sequence reads (using barcodes reads (plurality) can be sorted using a computer processor (memory), then assembled into contigs based on the barcodes; figures 1, 2, 3; column 3, lines 18-24). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the assembly of sequence reads to produce contigs, as previously described by Kennedy, as the previous disclosure by Li includes identifying low-level mutations in sequences, and the Kennedy reference includes identifying mutations based on alignments to references (Kennedy; abstract), and the combination of these references would have resulted in the use of a superior method to evaluate a genetic test that would be capable of identifying mutations.

-***-Continued Within the Next Supplemental Box-***-

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
-***-Continued from Previous Supplemental Box-***-

As per claim 11, Li, Selifonov, and Kennedy, in combination, disclose the method of claim 10, but Li does not disclose wherein the computer is operable to detect a mutation and report the mutation in relation to a reference. Kennedy discloses wherein the computer is operable to detect a mutation and report the mutation in relation to a reference (each mutation identified here can be described with reference to the reference genome using a computer; figures 1, 2, 3; column 3, lines 63-64). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of evaluating a genetic test, as previously disclosed by Li, with the assembly of sequence reads to produce contigs, as previously described by Kennedy, as the previous disclosure by Li includes identifying low-level mutations in sequences, and the Kennedy reference includes identifying mutations based on alignments to references (Kennedy; abstract), and the combination of these references would have resulted in the use of a superior method to evaluate a genetic test that would be capable of identifying mutations.

Claim 4 lacks an inventive step under PCT Article 33(3) as being obvious over Li and Selifonov and in further view of EP 1,321,477 B1 to Grawunder, et al. (hereinafter 'Grawunder').

As per claim 4, Li and Selifonov, in combination, disclose the method of claim 1, but Li does not disclose wherein the simulated mutation comprises two mutations in cis. Grawunder discloses wherein the simulated mutation comprises two mutations in cis (in order to use the selected cells for antibody production it must be prevented that further productive endogenous Ig gene rearrangements can be performed in these cells, and this can be done by mutating cis on both alleles of the IgH and IgL (two mutations); page 5 lines 24-27). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method for evaluating a genetic test, as previously disclosed by Li, with the cis mutations, as previously described by Grawunder, as the previous disclosure by Li includes the testing of a DNA library (Li; page, 10, right column, third paragraph) and the Grawunder reference includes the use of exons encoding variable domains derived from a library of diverse arrangements (Grawunder; page 17, lines 32-33), and the combination of these references would have resulted in the use of a simulated mutation comprising two mutations in cis that would allow for better detection of low-frequency mutations such as cis mutations.

Claims 1-11 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference GSGE-012/01WO 29258/62	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 13/61691	International filing date *(day/month/year)* 25 September 2013 (25.09.2013)
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 10 JAN 2014
Applicant's or agent's file reference GSGE-012/01WO 29258/62	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 13/61691	International filing date *(day/month/year)* 25 September 2013 (25.09.2013)
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300
Facsimile No. 571-273-3201	Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-012/01WO 29258/62	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 13/61691	International filing date *(day/month/year)* 25 September 2013 (25.09.2013)	(Earliest) Priority Date *(day/month/year)* 28 September 2012 (28.09.2012)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

Petitioner Illumina, Inc., EX1003, p. 610

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/61691

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

Petitioner Illumina, Inc., EX1003, p. 611

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/61691

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; C40B 20/00, 40/00 (2013.01)
USPC - 435/6.1, 6.12; 506/2, 13
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 435/6.1, 6.12; 506/2, 13

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/6.1, 6.12; 506/2, 13 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PatBase; Google Patents, Google Scholar Search terms: biomarker or gene marker, sensitivity, specificity, receiver operator curve (ROC), mutation panel, causal mutation, deleteriousness clinical significance, genetic counseling, autosomal recessive, causal mutation, deleteriousness, bystander mutation, CFTR, BLM, HEXA, ASP

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	YU et al. A novel set of DNA methylation markers in urine sediments for sensitive/specific detection of bladder cancer. Clin Cancer Res 15 December 2007 Vol 13 No 24 Pages 7296-7304. Especially abstract, pg 7296 col 2 para 2, pg 7299 col 1 para 1, pg 7300 fig 2, pg 7301 col 2 para 1, pg 7302 table 2, pg7303 fig 3.	1, 2, 5-13, 15-18 ---------- 3, 4, 14, 19, 20, 21
Y	US 2011/0098193 A1 (KINGSMORE et al.) 28 April 2011 (28.04.2011). Especially para [0050], [0234], [0243], [0248].	3, 4, 14, 19, 20, 21
Y	CASTELLANI et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros May 2008 Vol 7 No 3 Pages 179-196. Especially pg 181 col 2 para 2, pg 181 table 1, pg 182 table 2.	20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 2013 (13.12.2013)	10 JAN 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	10 JAN 2014
Applicant's or agent's file reference GSGE-012/01WO 29258/62	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 13/61691	25 September 2013 (25.09.2013)	28 September 2012 (28.09.2012)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68; C40B 20/00, 40/00 (2013.01)
USPC - 435/6.1, 6.12; 506/2, 13

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	13 December 2013 (13.12.2013)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/61691

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☒ in electronic form

   b. (time)

      ☒ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/61691

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	3, 4, 14, 19, 20, 21	YES
	Claims	1, 2, 5-13, 15-18	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-21	NO
Industrial applicability (IA)	Claims	1-21	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 2, 5-13 and 15-18 lack novelty under PCT Article 33(2) as being anticipated by the publication titled "A novel set of DNA methylation markers in urine sediments for sensitive/specific detection of bladder cancer" by Yu et al. (hereinafter "Yu").

As to claim 1, Yu teaches a method for optimizing an assay, the method comprising the steps of:
selecting a range (pg 7302 table 4; range 4-11 genes), having a minimum number and a maximum number, of predictive biomarkers for inclusion in a screening assay (pg 7303 fig 3; Receiver operating characteristics of the informative sets for bladder cancer detection. Both sensitivity (%),TP/ (TP + FN) (column 4,Table 4), and specificity (%),TN / (TN + FP) (column 5,Table 4) of each gene sets were calculated and plotted. TP, true positive; FN, false negative; FP, false positive; TN, true negative"; pg 7302 table 4-" Receiver operating characteristics of the informative sets for bladder cancer detection"; pg 7301, col 1, para 2 to col 2, para 1, Therefore, methylation profiling these four genes together should detect more bladder cancer in 100% specificity than when fewer genes were tested; The sensitivity continues to improve with the addition of ALX4 in 7-gene (sensitivity 87.1%), of CDH13 in 8-gene (88.6%), of RPRM in 9-gene (90.2%), of MINT in 10-gene (90.9%), and of BRCA1 in 11-gene (91.7%) sets with 87.6% specificity remaining.) such that use of fewer than said minimum number results in a reduction in sensitivity (pg 7301, col 1, para 2 to col 2, para 1, Therefore, methylation profiling these four genes together should detect more bladder cancer in 100% specificity than when fewer genes were tested) and use of greater than said maximum number results in a reduction in specificity (pg 7301, col 1, para 2 to col 2, para 1, An inclusion of RASSF1A that was found in 2 (8.7%) of 23 cases in the noncancerous urinary group (2 false positives and 21 true negatives; Table 4, column 3), in the five-gene set improves the sensitivity to 85.6%, but compromises specificity to 91.3% (Table 4, columns 4 and 5)) and conducting the assay using a number of biomarkers within said range (pg 7301, col 1, para 2 to col 2, para 1, The sensitivity continues to improve with the addition of ALX4 in 7-gene (sensitivity 87.1%), of CDH13 in 8-gene (88.6%), of RPRM in 9-gene (90.2%), of MINT in 10-gene (90.9%), and of BRCA1 in 11-gene (91.7%) sets with 87.6% specificity remaining.).

As to claim 2, Yu further teaches that the biomarker is a gene (pg 7302 table 4; e.g. SALL3, CFTR, ABCC6).

As to claim 5, Yu teaches that the biomarker is a gene product (pg 7296 col 2 para 2; "The use of a number of the overexpressed proteins in cancer tissues and/or urine identified by proteomic profiling, including the nuclear matrix protein 22 in urine, has also been tested in bladder cancer screening").

As to claim 6, Yu teaches that the gene product is RNA or protein (pg 7296 col 2 para 2; "The use of a number of the overexpressed proteins in cancer tissues and/or urine identified by proteomic profiling, including the nuclear matrix protein 22 in urine, has also been tested in bladder cancer screening").

As to claim 7, Yu teaches that the screening assay is used to determine the existence of a disease (pg 7302 table 4; bladder cancer detection; (pg 7301 col 2 para 1; "Therefore, methylation profiling these four genes together should detect more bladder cancer in 100% specificity than when fewer genes were tested. The sensitivity was 58.3% (77 of 132) for SALL3 alone; 74.2% (98 of 132) for SALL3 and CFTR; 80.3% (106 of 132) for SALL3, CFTR, and ABCC6; and 82.6% (109 of 132) for SALL3, CFTR, ABCC6, and HPR1 together")

As to claim 8, Yu teaches that the disease is cancer (pg 7302 table 4; pg 7301 col 1 para 1; bladder cancer).

As to claim 9, Yu teaches that the biomarker is associated with a disease is cancer (pg 7302 table 4; pg 7301 col 1 para 1; bladder cancer).

As to claim 10, Yu further teaches obtaining from a mammal a sample that comprises the selected biomarker (pg 7299 col 1 para 1; "DNA of morning urine samples were collected")

As to claim 11, Yu further teaches that the sample is body fluid (pg 7299 col 1 para 1; "DNA of morning urine samples were collected")

As to claim 12, Yu further teaches that prior to conducting the assay, the method further comprises enriching the sample for the biomarker (pg 7299 col 1 para 1; "DNA preparation from frozen tissues or urine sediments were made using the conventional proteinase K/organic extraction method as previously described").

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/61691

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V-2 (Citations and Explanations)

As to claim 13, Yu further teaches that the range is optimized for an ethnic group selected from: Asian/Pacific Islander (abstract; Interestingly, the cluster of reported methylation markers used in the U.S. bladder cancers is distinctly different from that identified in this study, suggesting a possible epigenetic disparity between the American and Chinese cases").

As to claim 15, Yu further teaches that the reduction in sensitivity is a statistically significant reduction in sensitivity (pg 7302 table 4 column: Statistical significance).

As to claim 16, Yu further teaches that the reduction in specificity is a statistically significant reduction in specificity (pg 7302 table 4; column Statistical significance).

As to claim 17, Yu teaches a method for optimizing an assay, the method comprising the steps of:
selecting a screening assay (pg 7302 table 4; bladder cancer methylation assay), wherein the screening assay screens biomarkers (pg 7302 table 4; different panels of 4-11 genes indicated) selecting a threshold specificity for the assay (pg 7300 fig 2; methylation levels of different genes); increasing the sensitivity of the assay by increasing the number of biomarkers used in the assay until the threshold sensitivity is reached with a range of biomarkers (pg 7301, col 1, para 2 to col 2, para 1, The sensitivity continues to improve with the addition of ALX4 in 7-gene (sensitivity 87.1%), of CDH13 in 8-gene (88.6%), of RPRM in 9-gene (90.2%), of MINT in 10-gene (90.9%), and of BRCA1 in 11-gene (91.7%) sets with 87.6% specificity remaining.) and conducting the assay using a number of biomarkers within said range (pg 7301, col 1, para 2 to col 2, para 1, pg 7302 table 4).

As to claim 18, Yu teaches screening assay, comprising a number of predictive biomarkers chosen to result in about 85% to 100% assay sensitivity and that does not reduce the specificity of the assay below about 80%. (pg 7301, col 1, para 2 to col 2, para 1, The sensitivity continues to improve with the addition of ALX4 in 7-gene (sensitivity 87.1%), of CDH13 in 8-gene (88.6%), of RPRM in 9-gene (90.2%), of MINT in 10-gene (90.9%), and of BRCA1 in 11-gene (91.7%) sets with 87.6% specificity remaining.).

Claims 3, 4, 14, 19 and 21 lack an inventive step under PCT Article 33(3) as being obvious over Yu, in view of US 2011/0098193 A1 to KINGSMORE et al. (hereinafter "Kingsmore")

As to claim 3, Yu teaches wherein the assay comprises sequencing at least a portion of the gene (pg 7297 fig 1), but does not teach sequencing to determine the presence or absence of a mutation. However, Kingsmore teaches sequencing to determine the presence or absence of a mutation, while maintaining certain levels of sensitivity and specificity (para [0234]; "Optimal genotyping cut-offs were 14% and 86% (FIG. 21B). With these cutoffs and a requirement for 20x coverage and 10 reads of quality greater/equal 20 to call a variant, the accuracy of sequence-based SNP genotyping was 98.8%, sensitivity was 94.9% and specificity was 99.99%. The positive predictive value (PPV) of sequence-based SNP"). An artisan of ordinary skill in the art would have readily appreciated that sequencing based assays can be conducted to detect disease markers based on mutation. Consequently, it would have been obvious for one of ordinary skill in the art to combine the use of sequencing in an assay, as taught by Yu, with sequencing that is used to determine the presence or absence of a mutation, as taught by Kingsmore, because it would have enabled a method to use sequencing to identify disease markers based on sequencing results.

As to claim 4, Kingsmore further teaches that the mutation is selected from the group consisting of: a single nucleotide polymorphism (para [0234]).

As to claim 14, Yu teaches that the range is optimized for an ethnic group (abstract). Yu does not teach the range is optimized for the genetic disposition of an individual. However, Kingsmore teaches that the range can be optimized for the genetic disposition of an individual (para [0050]; "However, to uncover the causative genetic components relevant to individual, personalized medicine, a move from the statistical to the determinate is desired. Regarding complex diseases, if there is insufficient homogeneity of causal elements among affected individuals to enable detection of statistical differences, then a move from the statistical to the determinate is also desired"). An artisan of ordinary skill in the art would have readily appreciated that the range of biomarkers or a mutation panel selected could be tailored to an individual's genetic predisposition, based on history of disease in a family, etc. Consequently, it would have been obvious for an artisan to combine a biomarker screen with the gene panel is optimized, as taught by Yu, with the range is optimized based on the genetic disposition of an individual, as taught by Kingsmore, because it would have enabled personalized medicine.

As to claim 19, Although Yu includes the CFTR gene, which is responsible for cystic fibrosis (CF), in the biomarker panel utilized in the screen (see pg 7302 table 4), Yu does not specifically teach the screening assay is a cystic fibrosis screening assay. However, Kingsmore teaches that the screening assay is a cystic fibrosis screening assay para [0243]; "As exemplified by cystic fibrosis, the carrier incidence and mutation spectrum of individual recessive disorders vary widely among populations. However, while group sizes were small, no significant differences in total carrier burden were found between Caucasians and other ethnicities nor between males and females"; para [0248]; Validation can be conducted. Addressing issues of specificity and false positives are complex when hundreds genes are being sequenced simultaneously. For certain diseases, such as cystic fibrosis, reference sample panels and metrics have been established). An artisan of ordinary skill in the art would have readily appreciated that CF was an autosomal recessive disease caused by a defect(s) in a single gene, and therefore would have been a disease that was very accessible to genetic testing. Consequently, it would have been obvious for one of ordinary skill in the art to combine a screening assay, as taught by Yu, with the screening assay is a cystic fibrosis screening assay, as taught by Kingsmore, because it would have enabled a genetic screening assay for mutations in a single gene.

As to claim 21, Kingsmore further teaches that the predictive biomarkers are mutations in the CFTR gene (para [0248]).

----------continued in next Supplemental Box----------

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/61691

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

Claim 20 lacks an inventive step under PCT Article 33(3) as being obvious over Yu, in view of Kingsmore, in further view of the publication titled " Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice" by Castellani et al. (hereinafter "Castellani").

As to claim 20, Kingsmore teaches a screening assay for cystic fibrosis (para [0243], [0248]). Neither Yu nor Kingsmore teaches the number of predictive biomarkers ranges between 500 to 700 biomarkers. However, Castellani teaches more than 1600 mutations catalogued in the CFTR gene, the gene with causal mutations for cystic fibrosis (pg 181 col 2 para 2; "To date more than 1500 sequence alterations have been identified in the CFTR gene and their listing is continuously updated within the Cystic Fibrosis Genetic Analysis Consortium (CFGAC) database [4]. In the database missense mutations account for 42%, frameshift for 15%, splicing for 12%, nonsense for around 10%, inframe insertions/deletions for 2%, large insertions/deletions for 3%, promoter mutations for 0.5%, and sequence variations which are not predicted to be disease-causing for 15% of all alleles"; pg 181 table 1; pg 182 table 2). An artisan of ordinary skill in the art would have readily appreciated that considering the fact that more than 1500 mutations in CFTR have been reported, where only about 15% have been verified not to be causal of some form of CFTR, as taught by Castellani, it would have been obvious for one of ordinary skill in the art to maintain a panel of between 500 and 700 biomarkers for screening persons. Consequently, it would have been obvious for an artisan of ordinary skill in the art to combine a screening assay for cystic fibrosis, as taught by Kingsmore, with the number of predictive biomarkers ranges between 500 to 700 biomarkers, as taught by Castellani, in view of the perspective of an artisan of ordinary skill in the art, because it would have enable predicting most circumstances where a particular inidividual is a carrier of a deleterious mutation in an assay with high sensitivity and specificity.

Claims 1-21 have industrial applicability as defined in PCT Article 33(4) because the subject matter can be made or used by industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	12 AUG 2013
Applicant's or agent's file reference GSGE-009/01WO 29258/54	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2013/036575	International filing date *(day/month/year)* 15 April 2013
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-009/01WO 29258/54	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2013/036575	International filing date *(day/month/year)* 15 April 2013	(Earliest) Priority Date *(day/month/year)* 16 April 2012
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/036575

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)
   - ☒ on paper
   - ☒ in electronic form

   b. (time)
   - ☐ in the international application as filed
   - ☐ together with the international application in electronic form
   - ☒ subsequently to this Authority for the purposes of search

2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/036575

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2013.01).
USPC - 435/6.11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C12N 15/10, 15/11; C12P 19/34; C12Q 1/68; C40B 40/08 (2013.01)
USPC - 435/6.1, 6.11, 91.1; 506/2, 7, 16; 702/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC Class/Subclass(es): C12Q 1/6869, 1/6876, 1/6883, 1/701

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patents, Google, Pubmed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/126614 A2 (PORRECA et al) 04 November 2010 (04.11.2010) entire document	1-6, 9-15, 18
---		---
Y		7, 8, 16, 17, 19, 20
Y	EP 1564306 A2 (MCGALL et al) 17 August 2005 (17.08.2005) entire document	7, 8, 16, 17, 19, 20
A	WO 2012/040387 A1 (MYLLYKANGAS et al) 29 March 2012 (29.03.2012) entire document	1-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2013	12 AUG 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	12 AUG 2013
Applicant's or agent's file reference GSGE-009/01WO 29258/54	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2013/036575	15 April 2013	16 April 2012

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2013.01)
USPC - 435/6.11

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	23 July 2013	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2013/036575

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☒ on paper

      ☒ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☒ subsequently to this Authority for the purposes of search

4. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2013/036575

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	3, 4, 7, 8, 12, 13, 16, 17	YES
	Claims	1, 2, 5, 6, 9-11, 14, 15, 18	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1, 2, 5, 6, 9-11, 14, 15 and 18 lack novelty under PCT Article 33(2) as being anticipated by Porreca et al. (hereafter Porreca).

Regarding Claim 1, Porreca discloses a method of improving performance of molecular inversion probe capture reactions (In other embodiments, methods improve allelic representation in a capture pool and, thus, improve variant detection outcomes, Pg. 32, Lns. 30-32; capturing target nucleic acids from a genomic sample of the subject with molecular inversion probes, Pg. 9, Lns. 15-16; methods include molecular inversion probe capture reactions, Pg. 22, Lns. 32-33), the method comprising: obtaining a nucleic acid (Invention provides a method of obtaining a nucleic acid preparation, Pg. 23, Lns. 18-19); fragmenting the nucleic acid into nucleic acid fragments (Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument; DNA should be sheared into fragments, Pg. 77, Lns. 11-12); and capturing a target on a nucleic acid fragment with a molecular inversion probe (Capturing target nucleic acids from a genomic sample of the subject with molecular inversion probes, Pg. 9, Lns. 15-16; DNA should be sheared into fragments, Pg. 77, Ln.12).

Regarding Claim 2, Porreca discloses the method of claim 1, further comprising the step of denaturing the nucleic acid or at least one nucleic acid fragment prior to the capturing step (Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument; DNA should be sheared into fragments, Pg. 77, Lns. 11-12; heat reaction to 95C for 5 min to denature genomic DNA, Pg. 75, Lns. 20-26 (nucleic acids are denatured prior to capture reaction); prior to performing a gene capture reaction, Pg. 44, Ln. 2).

Regarding Claim 5, Porreca discloses the method of claim 1, wherein the nucleic acid is selected from the group of genomic DNA, genomic RNA, whole or partial genome amplification product, high molecular weight DNA, and high molecular weight RNA (An experiment utilizing 1 ug of genomic DNA, Pg. 42, Ln. 20).

Regarding Claim 6, Porreca discloses the method of claim 1, wherein the step of fragmenting comprises mechanical fragmenting, chemical fragmenting, or enzymatic fragmenting (Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument; DNA should be sheared into fragments, Pg. 77, Lns. 11-12).

Regarding Claim 9, Porreca discloses the method of claim 2, wherein the step of denaturing comprises pH-based denaturing, heat-based denaturing, exonuclease degradation, or endonuclease nicking (Exonuclease digestion of non-circularized material is performed, Pg. 60, Ln. 21).

Regarding Claim 10, Porreca discloses a method of improving performance of capture reactions (In other embodiments, methods improve allelic representation in a capture pool and, thus, improve variant detection outcomes, Pg. 32, Lns. 30-32; capturing target nucleic acids from a genomic sample of the subject with molecular inversion probes, Pg. 9, Lns. 15-16; methods include molecular inversion probe capture reactions, Pg. 22, Lns. 32-33), the method comprising: obtaining a genomic nucleic acid (An experiment utilizing 1 ug of genomic DNA, Pg. 42, Ln. 20; invention provides a method of obtaining a nucleic acid preparation, Pg. 23, Lns. 18-19); fragmenting the genomic nucleic acid into nucleic acid fragments; contacting a probe to a nucleic acid fragment (Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument; DNA should be sheared into fragments, Pg. 77, Lns. 11-12; contacting a nucleic acid sample with a preparation of a probe e.g., a MIP [molecular inversion probe], Pg. 19, Ln.23), the probe comprising at least two target arms designed to hybridize upstream and downstream of a target sequence located on the nucleic acid fragment; and isolating the target sequence between the target arms; and analyzing the target sequence (Targeting arms of a probe that is designed to capture the target region or sequence thereof, Pg. 12, Lns. 11-12; both targeting arms may be designed to hybridize several bases or more upstream or downstream from the repeat region in such a way that the captured sequence includes a region of unique genomic sequence that on one or both sides of the repeat region; this unique region can then be used to identify the captured target e.g., based on sequence or hybridization information, Pg. 12, Lns. 20-24; associating unique sequence tags referred to as differentiator tag sequences with individual target molecules that are independently captured and/or analyzed, Pg. 39, Lns. 21-23).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2013/036575

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding Claim 11, Porreca discloses the method of claim 10, further comprising the step of denaturing the genomic nucleic acid or at least one nucleic acid fragment prior to the contacting step (Heat reaction to 95C for 5 min to denature genomic DNA (nucleic acids are denatured prior to contacting), Pg. 75, Ln. 25; prior to performing a gene capture reaction, Pg. 44, Ln. 2; wherein the target nucleic acid is a captured genomic locus, Pg. Ln. 3; analyzing a plurality of genetic loci are provided; the methods comprise contacting each of a plurality of target nucleic acids, Pg. 5, Lns. 26-28).

Regarding Claim 14, Porreca discloses the method of claim 10, wherein the nucleic acid is selected from the group of genomic DNA, genomic RNA and whole or partial genome amplification product (An experiment utilizing 1 ug of genomic DNA, Pg. 42, Ln. 20).

Regarding Claim 15, Porreca discloses the method of claim 10, wherein the step of fragmenting comprises mechanical fragmenting, chemical fragmenting, or enzymatic fragmenting (Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument; DNA should be sheared into fragments, Pg. 77, Lns. 11-12).

Regarding Claim 18, Porreca discloses the method of claim 10, wherein the step of denaturing comprises pH-based denaturing, heat-based denaturing, exonuclease degradation, or endonuclease nicking (Exonuclease digestion of non-circularized material is performed, Pg. 60, Ln. 21).

Claims 3, 4, 12, and 13 lack an inventive step under PCT Article 33(3) as being obvious over Porreca et al. (hereafter Porreca).

Regarding Claim 3, Porreca discloses the method of claim 1, but Porreca fails to explicitly disclose wherein the nucleic acid fragments are from about 5kb to about 100kb in length.
However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include nucleic acid fragments from about 5kb to about 100kb in length, since where the general conditions of the claim are disclosed in the prior art, discovering the optimum range involves only routine skill in the art. The motivation for doing so would be to ensure that longer target regions and sub-regions of genomic DNA are captured by probes in order to analyze the full target.

Regarding Claim 4, Porreca discloses the method of claim 1, wherein the nucleic acid fragments are about 1kb in length or more (Probes can be designed to capture targets [nucleic acids] having lengths in the range of up to 10, 20, 30.....1000, or more bps, [wherein 1000 base pair is equivalent to 1kb], Pg. 34, Lns. 7-8; DNA should be sheared into fragments, Pg. 77, Ln.12), but fails to explicitly disclose wherein the nucleic acid fragments are from about 1kb to about 10kb in length.
However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include nucleic acid fragments from about 1kb to about 10kb in length, since where the general conditions of the claim are disclosed in the prior art, discovering the optimum range involves only routine skill in the art. The motivation for doing so would be to ensure that longer target regions and sub-regions of genomic DNA are captured by probes in order to analyze the full target.

Regarding Claim 12, Porreca discloses the method of claim 10, but Porreca fails to explicitly disclose wherein the nucleic acid fragments are from about 5kb to about 100 kb in length.
However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include nucleic acid fragments from about 5kb to about 100kb in length, since where the general conditions of the claim are disclosed in the prior art, discovering the optimum range involves only routine skill in the art. The motivation for doing so would be to ensure that longer target regions and sub-regions of genomic DNA are captured by probes in order to analyze the full target.

Regarding Claim 13, Porreca discloses the method of claim 10, wherein the nucleic acid fragments are about 1kb in length or more (Probes can be designed to capture targets [nucleic acid] having lengths in the range of up to 10, 20, 30.....1000, or more bps, [wherein 1000 base pairs is equivalent to 1kb], Pg. 34, Lns. 7-8; DNA should be sheared into fragments, Pg. 77, Ln.12), but fails to explicitly disclose wherein the nucleic acid fragments are from about 1kb to about 10kb in length.
However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include nucleic acid fragments from about 1kb to about 10kb in length, since where the general conditions of the claim are disclosed in the prior art, discovering the optimum range involves only routine skill in the art. The motivation for doing so would be to ensure that longer target regions and sub-regions of genomic DNA are captured by probes in order to analyze the full target.

Claims 7, 8, 16, 17, 19 and 20 lack an inventive step under PCT Article 33(3) as being obvious over Porreca et al. (hereafter Porreca) in view of McGall et al. (hereafter McGall).

Regarding Claim 7, Porreca discloses the method of claim 5, but Porreca fails to explicitly disclose wherein the chemical fragmenting comprises pH-based shearing.
However, McGall is in the field of methods and compositions for fragmenting DNA (abstract) and teaches chemical fragmenting comprising pH-based shearing (The DNA sample to be fragmented is in an aqueous solution containing a buffer that is neutral (pH greater than or equal to 6.0) at a temperature between 20 and 37°C but becomes acidic (pH less than 6.0) at a temperature between 80 and 105°C. In one aspect the buffer is a Tris (Tris hydroyxmethyl aminomethane) buffer solution, Para. [0006]; DNA is fragmented by chemical or thermal treatment, Para. [0007]; fragmentation of ds cDNA with Tris Buffer at high temperature, Para. [0085]).
It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Porreca to include chemical fragmenting comprising pH-based shearing as taught by McGall as preparation by fragmentation helps to reduce the complexity of the nucleic acid sample and allows more efficient hybridization to a target probe (McGall, Para. [0020] and [0049]).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2013/036575

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding Claim 8, Porreca discloses the method of claim 6, but Porreca fails to explicitly disclose wherein the pH-based shearing also denatures the nucleic acid.
However, McGall is in the field of methods and compositions for fragmenting DNA (abstract) and teaches pH-based shearing also denaturing the nucleic acid (The DNA sample to be fragmented is in an aqueous solution containing a buffer that is neutral (pH greater than or equal to 6.0) at a temperature between 20 and 37°C but becomes acidic (pH less than 6.0) at a temperature between 80 and 105° C. In one aspect the buffer is a Tris (Tris hydroyxmethyl aminomethane) buffer solution, Para. [0006]; DNA is fragmented by chemical or thermal treatment, Para. [0007]; fragmentation mixtures containing 10 mg ds cDNA, 10 mM Tris-HCl, pH 7.2 at room temperature were incubated at 95°C for 75, 90, 105 and 120 minutes, Para. [0086], [wherein the instant application the use of pH or heat during the fragmenting step can result in denatured nucleic acid fragments, Pg. 11, Lns. 10-11]).
It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Porreca to include pH-based shearing also denaturing the nucleic acid as taught by McGall as DNA preparation by fragmentation and heat denaturation at 95°C helps to reduce the complexity of the nucleic acid sample and allows more efficient hybridization to a target probe (McGall, Paras. [0020], [0049], [0086]).

Regarding Claim 16, Porreca discloses the method of claim 15, but Porreca fails to explicitly disclose wherein the chemical fragmentation comprises pH-based shearing.
However, McGall is in the field of methods and compositions for fragmenting DNA (abstract) and teaches chemical fragmenting comprising pH-based shearing (The DNA sample to be fragmented is in an aqueous solution containing a buffer that is neutral (pH greater than or equal to 6.0) at a temperature between 20 and 37°C but becomes acidic (pH less than 6.0) at a temperature between 80 and 105°C. In one aspect the buffer is a Tris (Tris hydroyxmethyl aminomethane) buffer solution, Para. [0006]; DNA is fragmented by chemical or thermal treatment, Para. [0007]; fragmentation of ds cDNA with Tris Buffer at high temperature, Para. [0085]).
It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Porreca to include chemical fragmenting comprising pH-based shearing as taught by McGall as preparation by fragmentation helps to reduce the complexity of the nucleic acid sample and allows more efficient hybridization to a target probe, (McGall, Paras. [0020] and [0049]).

Regarding Claim 17, Porreca discloses the method of claim 14, but Porreca fails to explicitly disclose wherein the pH-based shearing also denatures the nucleic acid.
However, McGall is in the field of methods and compositions for fragmenting DNA (abstract) and teaches pH-based shearing also denaturing the nucleic acid (The DNA sample to be fragmented is in an aqueous solution containing a buffer that is neutral (pH greater than or equal to 6.0) at a temperature between 20 and 37°C but becomes acidic (pH less than 6.0) at a temperature between 80 and 105° C. In one aspect the buffer is a Tris (Tris hydroyxmethyl aminomethane) buffer solution, Para. [0006]; DNA is fragmented by chemical or thermal treatment, Para. [0007]; fragmentation mixtures containing 10 mg ds cDNA, 10 mM Tris-HCl, pH 7.2 at room temperature were incubated at 95°C, Para. [0086], [wherein the instant application the use of pH or heat during the fragmenting step can result in denatured nucleic acid fragments, Pg. 11, Lns. 10-11]).
It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Porreca to include pH-based shearing also denaturing the nucleic acid as taught by McGall as DNA preparation by fragmentation and heat denaturation at 95°C helps to reduce the complexity of the nucleic acid sample and allows more efficient hybridization to a target probe, (McGall, Paras. [0020], [0049], [0086]).

Regarding Claim 19, Porreca discloses a method of preparing a library for sequencing (During a library preparation process, each nucleic acid molecule may be tagged with a unique differentiator tag sequence in a configuration that permits the differentiator tag sequence to be sequenced along with the target nucleic acid sequence of interest, Pg. 41, Lns. 3-5; methods for overcoming problems associated with systematic and random errors (bias) in genome capture, amplification and sequencing methods, Pg. 39, Lns. 6-8), the method comprising: amplifying a captured target nucleic acid to generate an amplicon (The target nucleic acid is a captured genomic locus of the subject, amplifying the molecular inversion probe capture products [nucleic acids], Pg. 9, Lns. 10-12; in the context of a multiplex nucleic acid amplification reaction, differentiator tag sequences provide a basis for differentiating between multiple independent, primary amplicons of a target nucleic acid, Pg. 40, Lns. 13-16), but Porreca fails to explicitly disclose performing a hydrolysis reaction on the amplicon in the presence of heat to fragment the amplicon.
However, McGall is in the field of methods and compositions for fragmenting DNA (abstract) and teaches performing a hydrolysis reaction on the amplicon in the presence of heat to fragment the amplicon (The DNA sample to be fragmented is in an aqueous solution containing a buffer that is neutral (pH greater than or equal to 6.0) at a temperature between 20 and 37°C but becomes acidic (pH less than 6.0) at a temperature between 80 and 105°C. In one aspect the buffer is a Tris (Tris hydroyxmethyl aminomethane) buffer solution, Para. [0006]; DNA is fragmented by chemical or thermal treatment, Para. [0007]; amplifying the sample to generate amplified DNA [amplicon], Pg. 18, Ln. 6; fragmentation can be accomplished by altering temperature and pH, Pg. 7, Lns. 2-5; chemical methods for fragmentation of nucleic acids that are known in the art. These methods include: hydrolytic methods, Para. [0058]).
It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Porreca to include performing a hydrolysis reaction on the amplicon in the presence of heat to fragment the amplicon as taught by McGall as fragmentation methods including heat and hydrolytic methods can be used to select fragments of a desired size range and may be further desirable to optimize the size of nucleic acid molecules for subsequent analysis and minimize three dimensional structure, (McGall, Para. [0007], [0049] and [0058]).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2013/036575

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding Claim 20, modified Porreca discloses the method of claim 19, but Porreca fails to explicitly disclose wherein the step of performing the hydrolysis reaction comprises incubating the amplicon in a Tris buffer having a pH range from about 7.5 to about 8.0 at a temperature of about 65°C for 16 hours.
However, McGall is in the field of methods and compositions for fragmenting DNA (abstract) and teaches the step of performing the hydrolysis reaction comprising incubating the amplicon in a Tris buffer having a pH range from about 7.5 to about 8.0 at a temperature of about 65°C for 16 hours (Amplifying the sample to generate amplified DNA [amplicon], Pg. 18, Ln. 6; the DNA is in a solution that includes about 10 mM Tris-HCl, pH ~7.2-7.5, Para. [0060]; the DNA is mixed with the buffer at a temperature within the first temperature range and then incubated at a temperature in the second temperature range; the buffer is acidic in the second temperature range and the DNA is fragmented, Para. [0063]; in a preferred embodiment the buffer is Tris-HCl, Para. [0064]; tris or phosphate buffer pH 7-8.5 at 65°C is used to fragment single and double stranded DNA, Para. [0076]; the fragmentation reaction was incubated at 65°C, Para. [0097]).
It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Porreca to include a step of performing the hydrolysis reaction comprising incubating the amplicon in a Tris buffer having a pH range from about 7.5 to about 8.0 at a temperature of about 65°C for 16 hours as taught by McGall as fragmentation using Tris buffer, heat at 65°C and hydrolytic methods can be used to select fragments of a desired size range and may be further desirable to optimize the size of nucleic acid molecules for subsequent analysis and minimize three dimensional structure (McGall, Para. [0007], [0049], [0058], [0064] and [0076]).

Claims 1-20 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2018-04-27
Name/Print	Thomas C. Meyers	Registration Number	36,989

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					
If you wish to add additional U.S. Patent citation information please click the Add button.						

U.S.PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					
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FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button								

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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	1	International Search Report and Written Opinion for PCT/US2013/044039 mailed 01 November 2013, (15 pages)	☐
	2	International Search Report and Written Opinion for PCT/US2015/056037 mailed 12/23/15; 11 pages	☐
	3	International Search Report and Written Opinion issued January 29, 2015 in counterpart PCT Application No. PCT/US14/61138	☐
	4	International Search Report and Written Opinion mailed 10 Jun 2013 for related application PCT/US13/33435 with an International filing date of 22 March 2013 (7 pages)	☐
	5	International Search Report and Written Opinion mailed December 2, 2015, for International Patent Application No. PCT/US2015/049132 with Internaional Filing Date September 9, 2015 (14 pages)	☐
	6	International Search Report and Written Opinion mailed January 22, 2016, for International Patent Application No. PCT/US2015/050964, filed September 18, 2015 (6 pages).	☐
	7	International Search Report and Written Opinion mailed January 7, 2015, for International Patent Application No. PCT/US14/60256, filed October 13, 2014 (9 pages)	☐
	8	International Search Report and Written Opinion mailed May 4, 2016, for International patent application No. PCT/US2016/012886 with international filing date January 6, 2015 (7 pages)	☐
	9	International Search Report and Written Opinion mailed November 16, 2015, for International Application No. PCT/US2015/045247 with International Filing Date August 14, 2015 (10 pages)	☐
	10	International Search Report and Written Opinion mailed on January 29, 2015, for Patent Application No. PCT/US14/61138, filed October 17, 2014, (11 pages)	☐
	11	International Search Report and Written Opinion mailed on January 29, 2015, for Patent Application No. PCT/US2014/060056, filed October 10, 2014, (14 pages)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

	12	International Search Report and Written Opinion mailed on June 28, 2013, for Patent Application No. PCT/US2013/032885, filed March 19, 2013, (9 pages)	☐
	13	International Search Report and Written Opinion mailed on March 18, 2015, for Patent Application No. PCT/US14/40516, filed June 2, 2014 (16 pages)	☐
	14	International Search Report and Written Opinion mailed on May 2, 2016, for International Patent Application No. PCT/US2016/013346, filed January 14, 2016 (7 pages).	☐
	15	International Search Report and Written Opinion mailed September 2, 2015 for International Patent Application No. PCT/US2015/030366, filed May 12, 2015 (12 pages)	☐
	16	International Search Report and Written Opinion mailed September 3, 2014, for International Patent Application No. PCT/US2014/027324, filed March 14, 2014, 7 pages.	☐
	17	International Search Report and Written Opinion of the International Searching Authority mailed December 13, 2016 for International Application No. PCT/US2016/051928 (14 Pages).	☐
	18	International Search Report and Written Opinion of the International Searching Authority mailed June 12, 2017 for International Application No. PCT/US2017/016498 (12 Pages).	☐
	19	International Search Report for PCT/US12/55362 mailed February 25, 2013, pg 15	☐
	20	Isosomppi, 2009, Disease causing mutations in the CLRN1 gene alter normal CLRN1 protien trafficking to the plasma membrane, Mol Vis 15:1806-1818	☐
	21	Isosomppi, 2009, Disease-causing mutations in the CLRN1 gene alter normal CLRN1 protein trafficking to the plasma membrane, Mol Vision 15:1806-1818	☐
	22	Jensen, 2001, Orthologs and paralogs—we need to get it right, Genome Biol 2(8):1002-1002.3	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
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	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

	23	Kambara et al., Optimization of Parameters in a DNA Sequenator Using Fluorescence Detection, Nature Biotechnology 6:816-821 (1988)	☐
	24	Kennedy et al., 2013, Accessing more human genetic variation with short sequencing reads, American Society of Human Genetics 63rd Annual Meeting, Abstract, October 22, 2013	☐
	25	Kerem, 1989, Identification of the cystic fibrosis gene: genetic analysis, Science 245:1073-1080	☐
	26	Kinde, 2012, FAST-SeqS: a simple an effective method for detection of aneuploidy by massively parallel sequencing, PLoS One 7(7):e41162	☐
	27	Kneen, 1998, Green fluorescent protein as a noninvasive intracellular pH indicator, Biophys J 74(3):1591-99	☐
	28	Koboldt, 2009, VarScan: variant detection in massively parallel sequencing of individual and pooled samples, Bioinformatics 25:2283-85	☐
	29	Li, 2003, DNA binding and cleavage by the periplasmic nuclease Vvn: a novel structure with a known active site, EMBO J 22(15):4014-4025	☐
	30	Li, 2010, Fast and accurate long-read alignment with Burrows-Wheeler transform, Bioinformatics 26(5):589-95.	☐
	31	Li, 2011, Improving SNP discovery by base alignment quality, Bioinformatics 27:1157	☐
	32	Li, 2012, A new approach to detecting low-level mutations in next-generation sequence data, Genome Biol 13:1-15	☐
	33	Li, 2014, HUGO: Hierarchical mUlti-reference Genome cOmpression for aligned reads, JAMIA 21:363-373	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
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	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

	34	Lin, 2008, ZOOM! Zillions Of Oligos Mapped, Bioinformatics 24:2431	☐
	35	Lin, 2010, A molecular inversion prove assay for detecting alternative splicing, BMC Genomics 11(712):1-14	☐
	36	Liu et al., 2012, Comparison of next-generation sequencing systems, ePub 2012(251364)	☐
	37	Llopis, 1998, Measurement of cytosolic, mitochondrial, and Golgi pH in single living cells with green fluorescent proteins, PNAS 95(12):6803-08	☐
	38	Ma, 2006, Application of real-time polymerase chain reaction (RT-PCR), J Am Soc 1-15	☐
	39	MacArthur, 2014, Guidelines for investigating causality of sequence variants in human disease, Nature 508:469-76	☐
	40	Maddalena, 2005, Technical standards and guidelines: molecular genetic testing for ultra-rare disorders, Genet Med 7:571-83	☐
	41	Malewicz, 2010, Pregel: a system for large-scale graph processing, Proc. ACM SIGMOD Int Conf Mgmt Data 135-46	☐
	42	McDonnell, "Antisepsis, disinfection, and sterilization: types, action, and resistance," pg. 239 (2007).	☐
	43	McKenna, 2010, The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data, Genome Res 20(9):1297-1303	☐
	44	Meyer, 2007, Targeted high-throughput sequencing of tagged nucleic acid samples, Nucleic Acids Research 35(15): e97 (5 pages).	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

	45	Meyer, 2008, Parallel tagged sequencing on the 454 platform, Nature Protocols 3(2):267-78.	☐
	46	Miesenbock, 1998, Visualizing secretion and synaptic transmission with pH-sensitive green fluorescent proteins, Nature 394(6689):192-95	☐
	47	Miller, 2010, Assembly algorithms for next-generation sequencing data, Genomics 95:315-327	☐
	48	Miyazaki, 2009, Characterization of deletion breakpoints in patients with dystrophinopathy carrying a deletion of exons 45-55 of the Duchenne muscular dystrophy (DMD) gene, J Hum Gen 54:127-30	☐
	49	Mohammed, 2012, DELIMINATE-a fast and efficient methods for loss-less compression of genomice sequences, Bioinformatics 28(19):2527-2529	☐
	50	Moudrianakis, 1965, Base sequence determination in nucleic acids with the electron microscope, III. Chemistry and microscopy of guanine-labeled DNA, PNAS 53:564-71	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

ENTERED IN CPI

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference GSGE-011/01WO 29258/55	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 13/44039	International filing date *(day/month/year)* 04 June 2013 (04.06.2013)
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 01 NOV 2013
Applicant's or agent's file reference GSGE-011/01WO 29258/55	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 13/44039	International filing date *(day/month/year)* 04 June 2013 (04.06.2013)
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-011/01WO 29258/55	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 13/44039	International filing date *(day/month/year)* 04 June 2013 (04.06.2013)	(Earliest) Priority Date *(day/month/year)* 04 June 2012 (04.06.2012)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the language, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

Petitioner Illumina, Inc., EX1003, p. 638

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/44039

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G06F 19/22, C12Q 1/68 (2013.01)
USPC - 702/20, 435/6.11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): G06F 19/22, C12Q 1/68 (2013.01)
USPC: 702/20, 435/6.11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 702/19, 435/6.12, 536/23.1
(keyword limited; terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar, Google Web, search terms used: clinical significance, variant sequence, sequence read, reference sequence, genetic profile, sequencing-by-synthesis, single molecule sequencing, equivalent indel region, insertion or deletion, tandem repeat, splice site frameshift mutation, functional region, DNA RNA eDNA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2011/0166029 A1 (MARGULIES et al.) 7 July 2011 (07.07.2011) para [0010], [0011], [0046], [0048], [0049], [0067], [0078], [0081], [0088], [0095], [0096], [0101], [0104]	1-6, 8, 9 ---------- 7, 10
Y	US 2009/0129647 A1 (DIMITROVA et al.) 21 May 2009 (21.05.2009) Abstract, para [0040]	7
Y	WO 2012/051208 A2 (NAZARENKO etal.) 19 April 2012 (19.04.2012) para [0007], [0009], [0040], [0041]	10

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2013 (14.10.2013)	01 NOV 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	01 NOV 2013
Applicant's or agent's file reference GSGE-011/01WO 29258/55	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 13/44039	04 June 2013 (04.06.2013)	04 June 2012 (04.06.2012)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G06F 19/22, C12Q 1/68 (2013.01)
USPC - 702/20, 435/6.11

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to th IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	14 October 2013 (14.10.2013)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/44039

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Petitioner Illumina, Inc., EX1003, p. 641

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/44039

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	7, 10	YES
	Claims	1-6, 8, 9	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-10	NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-6, 8 and 9 lack novelty under PCT Article 33(2) as being anticipated by US 2011/0166029 A1 to Margulies et al. (hereinafter 'Margulies').

Regarding claim 1, Margulies discloses a method for determining the clinical significance of a variant sequence (para [0010] "The method may comprise the steps of obtaining a nucleic acid ... from a subject and conducting an assay to identify whether there is a variant sequence in the subject's nucleic acid.", para [0011] "the invention may comprise methods for identifying mutations (i.e., variants) correlated with the presence or increased risk of developing an autism spectrum disorder.", para [0078] "The method may further include the steps of assessing the clinical significance of a variant or variants in the nucleic acid sequence ... for autism spectrum disorders."),
the method comprising: sequencing a nucleic acid to generate at least one sequence read (para [0046] "In some embodiments, the method may comprise obtaining a nucleic acid ... from a subject and sequencing at least a portion of a nucleic acid in order to obtain a sample nucleic acid sequence for at least one gene.");
identifying a variant sequence within the sequence read based on mapping the sequence read to a reference sequence (para [0081] "The nucleic acid may be sequenced ... in order to detect variants (i.e., mutations) in the nucleic acid compared to a reference sequence derived from one or more individuals not known to suffer from an autism spectrum disorder", para [0088] "In next generation (massively parallel sequencing), all regions of interest are sequenced together, and the origin of each sequence read is determined by comparison (alignment) to a reference sequence.");
determining the equivalent indel [i. e. insertion or deletion] region of the variant sequence (para [0101] "types of variants include deletions of one or more nucleotides ... insertions of one or more nucleotides");
identifying a functional region comprising at least a portion of the equivalent insertion/deletion region (para [0101] "As shown in Table 2, sequence variants are named according to the change they cause in the DNA sequence and the resultant change (if any) to the peptide sequence.", para [0104] "Frameshift mutations cause a shift in reading frame leading to a complete change of the amino acid sequence downstream of the mutation (i.e., the frameshift site). A frameshift mutation is caused by a net deletion or insertion of a number of nucleotides not divisible by 3."),
associating the equivalent indel region with the identified functional region, thereby to determine clinical significance of the variant (para [0101] "types of variants include deletions of one or more nucleotides ... insertions of one or more nucleotides", para [0095] "As depicted in FIG. 2, the variants and/or variant combinations may be assessed for their clinical significance for autism spectrum disorders based on one or more of the following methods. If a variant or a variant combination is reported or known to occur more often in nucleic acid from subjects with, than in subjects without, autism spectrum disorders, it is considered to be at least potentially predisposing to autism spectrum disorders. ... Conversely, if a variant is found in both populations at a similar frequency, it is less likely to be associated with the development of an autism syndrome disorder (ASD)", para [0096] " if a variant or a variant combination is predicted to have an overall deleterious effect on a protein or gene expression (i.e., resulting in a nonsense mutation, a frameshift mutation, or a splice site mutation ...), based on the predicted effect on the sequence and/or the structure of a protein or a nucleic acid ... it is considered to be at least potentially predisposing to autism spectrum disorders").

Regarding claim 2, Margulies further teaches nucleic acid that is DNA and RNA (para [0067] "The techniques for sequencing nucleic acids (both DNA and RNA) are highly sensitive and therefore, can be used almost any biological sample (i.e., tissue or body fluid) taken from subject.").

Regarding claim 3, Margulies further teaches sequencing that is sequencing-by-synthesis (para [0048] "In various embodiments of the methods of the invention ... the assay comprises ... nucleic acid sequencing ... Additionally and/or alternatively, the sequencing comprises at least one of single-molecule sequencing-by-synthesis.").

----------SEE FIRST SUPPLEMENTAL BOX TO CONTINUE----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/44039

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V No. (2) Citations and Explanations:

Regarding claim 4, Margulies further teaches sequencing that is single molecule sequencing (para [0081] "The nucleic acid may be sequenced ... in order to detect variants (i.e., mutations) in the nucleic acid compared to a reference sequence ... sequence variants ... can be detected by any sequencing method known in the art e.g., ... single molecule sequencing").

Regarding claim 5, Margulies further teaches variant sequences that comprise a genetic mutation (para [0081] "The nucleic acid may be sequenced and/or its genomic arrangement and/or copy number is determined in order to detect variants (i.e., mutations) in the nucleic acid compared to a reference sequence derived from one or more individuals not known to suffer from an autism spectrum disorder").

Regarding claim 6, Margulies further teaches genetic mutations that are an insertion or a deletion (para [0101] "types of variants include deletions of one or more nucleotides ... insertions of one or more nucleotides", para [0104] "Frameshift mutations cause a shift in reading frame leading to a complete change of the amino acid sequence downstream of the mutation (i.e., the frameshift site). A frameshift mutation is caused by a net deletion or insertion of a number of nucleotides not divisible by 3.");

Regarding claim 8, Margulies further teaches determining a functional region that comprises a gene, an exon, an intron, a splice site, a regulatory element (para [0010] "The method may comprise the steps of obtaining a nucleic acid ... and conducting an assay to identify whether there is a variant sequence in the ... nucleic acid.", para [0049] "the nucleic acid in the conducting step comprises a gene ... an exon, an intron, a gene regulatory element ... including splice sites ... may be evaluated for mutations (i.e., variants).").

Regarding claim 9, Margulies further teaches variant sequences is a splice site mutation, a nonsense mutation, or a frameshift mutation (para [0096] "if a variant or a variant combination is predicted to have an overall deleterious effect on a protein or gene expression (i.e., resulting in a nonsense mutation, a frameshift mutation, or a splice site mutation, or even a missense mutation), based on the predicted effect on the sequence and/or the structure of a protein or a nucleic acid, and if this variant or variant combination affects a gene or genes known to be associated with autism spectrum disorders, it is considered to be at least potentially predisposing to autism spectrum disorders").

Claim 7 lacks an inventive step under PCT Article 33(3) as being obvious over Margulies in view of US 2009/0129647 A1 to Dimitrova (hereinafter 'Dimitrova').

Regarding claim 7, Margulies does not expressly teach identifying a genetic mutation that is located in a tandem repeat, however, Dimitrova teaches methods for said identifying (Abstract "Spectrogram extraction from DNA sequence has been known since 2001. ...Given a DNA sequence or whole genomes, with this method it is easy to generate a large number of spectrogram images. However, the difficult part is to elucidate where are the repetitive patterns and to associate a biological and clinical meaning to them. The present disclosure provides systems and methods that facilitate the location and/or identification of repetitive DNA patterns, such as ..tandem repeats", para [0040] "As described herein, exemplary systems and methods support and/or utilize one or more of the following DNA spectral analysis techniques: (i) comparative histogram methodologies; (ii) selection/classification using support vector machines and genetic algorithms; and (iii) spectrovideo methodologies based on spectrogram extractions from DNA sequence data. Many benefits may be realized according to the present disclosure, e.g., (i) enhanced visualization of genomic information, (ii) identification of repetitive DNA patterns, e.g. .. tandem repeats ...to permit rapid visualization of an entire genome at a desired resolution.). It would have been obvious to one of ordinary skill in the art to add Dimitrova's methods for identifying tandem repeat mutations among mutations in a nucleic acid, because said mutations are difficult to characterize, as taught by Dimitrova, but may add new clinically significant mutations to those identified by the method of Margulies.

Claim 10 lacks an inventive step under PCT Article 33(3) as being obvious over Margulies in view of WO 2012/051208 A2 to Nazarenko et al. (hereinafter 'Nazarenko').

Regarding claim 10, Margulies does not expressly teach determining whether the equivalent indel region extends beyond the functional region, however, Nazarenko teaches said determination (para [0007] "Embodiments of the present invention can provide identification of junctions (e.g., resulting from large-scale rearrangements) of a sequenced genome with respect to a human genome reference sequence.", para [0009] "a method is provided for determining whether a clinically significant junction exists between a sample genome and a reference genome", para [0040] "To determine a genome of an organism, fragments from a biological sample can have their two ends sequenced ... These mated pairs of sequence reads can then be mapped to one or more reference genomes to determine the sample genome. ... in some cases, pairs cannot be mapped as expected to a reference genome, and are called discordant pairs. ... Discordant mate pairs can occur when a rearrangement, or a large insertion or deletion, has occurred in the sample genome relative to the reference genome.", para [0041] "The accurate identification of rearrangement locations is important as such cases typically are the result of disease, such as cancer, ... Such rearrangement can include, for example ... a piece of the genome being deleted. Such rearrangements can cause the loss of a gene, a function of the gene, and a protein created from the gene."). It would have been obvious to one of ordinary skill in the art to combine Nazarenko's method of determining whether the equivalent indel region extends beyond the functional region with Margulies' method for determining the clinical significance of a variant sequence having smaller or uncharacterized indel mutations, because said determining could reveal other clinically significant aspects of extended indel regions, as taught by Nazarenko (para [0041] "since there are changes in which portions of the genome become near each other, a new expression or disregulation can occur. ... the discovery of larger insertions, deletions, duplications, and rearrangements can add value beyond the discovery of small variations.").

Claims 1-10 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

SEARCH HISTORY

Application Number	PCT/US 13/44039
Search Conducted By	EM
Search Approved By	PP

US/IPC Classifications Searched	IPC(8): G06F 19/22, C12Q 1/68 (2013.01) USPC: 702/20, 435/6.11
Date Conducted	11 October 2013 (11.10.2013)

Documentation Searched	USPC - 702/19, 435/6.12, 536/23.1 (keyword limited; terms below)
Search Terms Used	clinical significance, clinically significant, variant sequence, sequence read, reference sequence, mapping, genetic profile, sequencing-by-synthesis, single molecule sequencing, equivalent indel region, insertion or deletion, tandem repeat, splice site mutation frameshift mutation, functional region, exon intron mutation, DNA RNA eDNA
Date Conducted	12 October 2013 (12.10.2013), 13 October 2013 (13 10 2013)

Electronic Database Searched	PatBase
Files Searched	Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO Bibliographic: (Europe) AT BA BE BG CH CS CY CZ DD DK EE ES FI GE GR HR HU IE IS IT LT LU LV MC MD MT NL NO PL PT RO RS SE SI SK SM TR UA YU (Asia) EA GC HK ID IL IN KZ MN MY PH RU SG SU TH TJ TW UZ VN (North America) CA CR CU DO GT HN MX NI PA SV TT (South America) AR BR CL CO EC PE UY (Australasia) AU NZ (Africa) AP DZ EG KE MA MW OA ZA ZM ZW
Date Conducted	12 October 2013 (12.10.2013)
Search Logic:	

Search 1: IC=(G06F19/22 or C12Q1/68) (Results 94534)
Search 2: 1 and sequence near variant (Results 11307)
Search 3: 2 and clinical# near significant# (Results 1317)
Search 4: 3 and reference near sequence (Results 1016)
Search 5: 4 and map# (Results 839)
Search 6: 5 and DNA or RNA or eDNA (Results 839)
Search 7: 6 and next generation sequencing or NGS (Results 21)
Search 8: 5 and single molecule sequencing (Results 7)
Search 9: 5 and sequencing-by-synthesis (Results 8)
Search 10: 5 and insertion and deletion (Results 796)
Search 11: 10 and tandem repeat (Results 73)
Search 12: 11 and functional# (Results 73)
Search 12: 11 and functional near region (Results 6)
Search 13: 11 and frameshift and splice site (Results 13)
Search 14: UC=(702/20 or 435/6.11 or 702/19 or 435/6.12 or 536/23.1) (Results 38964)
Search 15: 14 and sequence near variant or mutation (Results 8399)
Search 16: 15 and clinical# near significant# (Results 751)
Search 17: 16 and map# (Results 550)
Search 18: 17 and reference near sequence (Results 396)
Search 19: 18 and insertion and deletion (Results 362)
Search 20: 19 and tandem repeat (Results 40)
Search 21: 20 and frameshift and splice site (Results 10)
Search 22: 15 and functional near region (Results 726)
Search 23: 22 and reference near sequence (Results 521)
Search 24: 23 and reference near sequence (Results 521)
Search 24: clinical# near significant# (Results 21177)
Search 24: 15 and clinical# near significant# (Results 751)
Search 24: 23 and clinical# near significant# (Results 82)
Search 25: 24 and tandem repeat (Results 5)
Search 26: 24 and insertion and deletion (Results 81)
Search 27: 26 and insertion and deletion (Results 81)
Search 27: 26 and frameshift (Results 61)
Search 28: 27 and splice site (Results 3)
Search 29: FT=(clinical near significant#) (Results 9874)
Search 30: 29 and sequence near variant or mutation (Results 1301)
Search 31: 30 and reference near sequence (Results 614)
Search 32: 31 and functional near region (Results 84)
Search 33: 32 and insertion and deletion (Results 69)
Search 34: 33 and frameshift (Results 8)

Search 35: 33 and splice site (Results 5)
Search 36: FT=(sequence near genomic region) (Results 469)
Search 37: 36 and profile (Results 212)
Search 38: 37 and functional# near region (Results 35)
Search 39: 38 and variant or mutation (Results 35)
Search 40: 39 and insertion and deletion (Results 33)
Search 41: 40 and frameshift (Results 5)
Search 42: 41 and splice site (Results 4)
Search 43: FT=(sequencing-by-synthesis or single molecule sequencing) (Results 1063)
Search 44: 43 and variant or mutation (Results 677)
Search 45: 44 and insertion and deletion (Results 267)
Search 46: 45 and frameshift and splice site (Results 16)
Search 47: 46 and human and disease (Results 16)
Search 48: FT=(equivalent and indel and region) (Results 441)
Search 49: 48 and clinical# (Results 253)
Search 50: 49 and variant or mutation (Results 243)
Search 51: 50 and significance (Results 173)
Search 52: 51 and functional# near region (Results 12)
Search 53: 52 and associat# (Results 11)
Search 54: FT=(map# and sequence read, and reference sequence) (Results 198)
Search 55: 54 and equivalent and indel and region (Results 14)
Search 56: 55 and insertion and deletion (Results 9)
Search 57: 56 and functional# near region (Results 1)
Search 58: 54 and sequencing-by-synthesis or single molecule sequencing (Results 80)

Electronic Database Searched	Google
Files Searched	Google Patents
Date Conducted	13 October 2013 (13 10 2013)

Search Logic:

method indel detection clinical significance	About 1,010 results (0.33 seconds)
GOOD START GENETICS, INC. sequence read	About 24,800 results (0.17 seconds)
method indel disease causing mutation clinical significance	About 676 results (0.28 seconds)
clinical significance mutation genome screen	About 58,800 results (0.23 seconds)
clinical significance mutation whole genome screen	About 56,600 results (0.28 seconds)
clinical significance equivalent indel region	About 3,000 results (0.28 seconds)
map mutation functional region clinical significance	About 120,000 results (0.31 seconds)
associate indel functional region clinical significance	About 4,370 results (0.29 seconds)
causative mutation exon intron splice site patient sample	About 53,000 results (0.39 seconds)

correlate indel functional region clinical significance About 3,010 results (0.31 seconds)
correlate variant identification clinical significance About 89,800 results (0.30 seconds)
disease gene identification clinical significance About 143,000 results (0.34 seconds)
disease gene identification sequence clinical significance About 48,700 results (0.25 seconds)
disease gene identification sequencing-by-synthesis About 279,000 results (0.25 seconds) disease gene identification single molecule sequencing About 549,000 results (0.30 seconds) indel functional region disease mutation About 25,900 results (0.30 seconds) indel functional region known genes About 52,400 results (0.30 seconds) clinical significance splice site mutation nonsense frameshift About 1,860 results (0.30 seconds) determining equivalent indel region variant sequence About 46,400 results (0.29 seconds) patient sample mutation indel clinical significance About 1,010 results (0.30 seconds) patient sample mutation equivalent indel region About 16,700 results (0.26 seconds)
clinical significance mutation algorithm About 34,100 results (0.23 seconds)
clinical significance mutation exome end sequencing About 132 results (0.35 seconds)

Electronic Database Searched	Google
Files Searched	Google Scholar
Date Conducted	13 October 2013 (13 10 2013)
Search Logic:	

clinical significance patient sequence variant About 364,000 results (0.11 sec)
clinical significance sequence variant About 839,000 results (0.12 sec)
clinical significance sequence variant reference sequence About 325,000 results (0.06 sec)
clinical significance sequence variant reference region About 195,000 results (0.16 sec)
clinical significance mutation About 1,520,000 results (0.10 sec)
clinical significance mutation genome screen About 76,900 results (0.16 sec)
clinical significance mutation whole genome screen About 45,900 results (0.19 sec)
clinical significance equivalent indel region About 17,700 results (0.18 sec)
clinical significance variant equivalent indel region About 7,480 results (0.16 sec)
patient sample mutation equivalent indel region About 7,600 results (0.05 sec)
patient sample mutation indel clinical significance About 12,200 results (0.23 sec)
whole genome sequence mutation indel clinical significance About 10,500 results (0.24 sec)
map mutation functional region clinical significance About 10,500 results (0.24 sec)
associate indel functional region clinical significance About 186,000 results (0.14 sec)
correlate indel functional region clinical significance About 17,800 results (0.21 sec)
indel functional region disease causing mutation About 18,900 results (0.37 sec)
indel functional region disease mutation About 19,400 results (0.21 sec)
causitive mutation exon intron splice codon patient sample About 7,650 results (0.08 sec)
clinical significance splice site mutation nonsense frameshift About 16,000 results (0.15 sec)
determining equivalent indel region variant sequence About 19,000 results (0.20 sec)

Electronic Database Searched	Google
Files Searched	Google Web
Date Conducted	13 October 2013 (13 10 2013)

Search Logic:

determining equivalent indel region variant sequence	About 24,400,000 results (0.11 seconds)
clinical significance patient sequence variant	About 3,410,000 results (0.34 seconds)
clinical significance splice site nonsense frameshift	About 207,000 results (0.33 seconds)
clinical significance sequence variant reference	About 2,900,000 results (0.34 seconds)
clinical significance mutation algorithm	About 5,370,000 results (0.29 seconds)
clinical significance mutation genome screen	About 2,300,000 results (0.27 seconds)
clinical significance mutation exome end sequencing	About 322,000 results (0.32 seconds)
whole genome sequence mutation indel	About 620,000 results (0.30 seconds)
map mutation functional region clinical significance	About 5,680,000 results (0.29 seconds)
patient sample mutation indel clinical significance	About 2,260,000 results (0.30 seconds)
patient sample mutation equivalent indel region	About 5,820,000 results (0.31 seconds)
patient sample mutation single molecule sequencing	About 6,000,000 results (0.29 seconds)
patient sample mutation sequencing-by-synthesis	About 7,280,000 results (0.28 seconds)
associate indel functional region clinical significance	About 13,000,000 results (0.33 seconds)
correlate indel functional region clinical significance	About 3,570,000 results (0.35 seconds)
indel functional region disease mutation	About 21,700,000 results (0.33 seconds)
indel functional region known genes	About 21,800,000 results (0.27 seconds)

SAO Supplemental Search

Electronic Database Searched	PatBase
Files Searched	Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO Bibliographic: (Europe) AT BA BE BG CH CS CY CZ DD DK EE ES FI GE GR HR HU IE IS IT LT LU LV MC MD MT NL NO PL PT RO RS SE SI SK SM TR UA YU (Asia) EA GC HK ID IL IN KZ MN MY PH RU SG SU TH TJ TW UZ VN (North America) CA CR CU DO GT HN MX NI PA SV TT (South America) AR BR CL CO EC PE UY (Australasia) AU NZ (Africa) AP DZ EG KE MA MW OA ZA ZM ZW
Date Conducted	16 October 2013 (16.10.2013)

Search Logic:
1) UC=(702/20 or 435/6.11 or 702/19 or 435/6.12 or 536/23.1) (38970) 2) IPC=(G06F19/22 or C12Q1/68) (94546) 3) (variant or mutation or insertion or deletion) w5 sequenc* (68192) 4) 3 and (1 or 2) (28573) 5) 3 and (clinical significance or clinical relevance) (1847) 6) 5 and tandem repeat (80) 7) 5 and (gene or exon or intron or splice site or codon or regulatory element or non-coding region) (1827) 8) 5 and ((splice site or in-frame or nonsense or unknown nucleic acid base or frameshift) w3 (mutation)) (72) 9) 6 and 7 and 8 (7) 10) (clinical significance or clinical relevance) w10 (variant or mutation or insertion or deletion) (75) 11) 10 and (1 or 2) (56) 12) 10 and (gene or exon or intron or splice site or codon or regulatory element or non-coding region) (73) 13) 12 and tandem repeat (5) 14) 12 and ((splice site or in-frame or nonsense or unknown nucleic acid base or frameshift) w3 (mutation)) (10) 15) 13 and 14 (0)

Electronic Database Searched	Google
Files Searched	Google Scholar
Date Conducted	16 October 2013 (16.10.2013)
Search Logic:	
("clinical significance" OR "clinical relevance") (variant OR mutation OR insertion OR deletion) About 17,900 results (0.08 sec) allintitle:(("clinical significance" OR "clinical relevance") (variant OR mutation OR insertion OR deletion)) About 270 results (0.10 sec)	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-029/01WO 29258/146	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2015/056037**	International filing date *(day/month/year)* **16 October 2015 (16.10.2015)**	(Earliest) Priority Date *(day/month/year)* 17 October 2014 (17.10.2014)
Applicant **GOOD START GENETICS, INC.**		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **4** sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

Petitioner Illumina, Inc., EX1003, p. 651

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/056037

A. CLASSIFICATION OF SUBJECT MATTER

C12Q 1/68(2006.01)i, G06F 19/20(2011.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q 1/68; C40B 20/00; C40B 40/06; G06F 19/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: pre-implantation genetic screening, aneuploidy detection, embryo, Z-score

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014-0206552 A1 (NATERA, INC.) 24 July 2014 See abstract; claims 1-7; paragraphs [0002]-[0045], [0128]-[0171], [0222]-[0234].	1-26
A	US 2012-0270212 A1 (RABINOWITZ et al.) 25 October 2012 See abstract; claims 1-43; and paragraph [0426].	1-26
A	US 2013-0288242 A1 (STOUGHTON et al.) 31 October 2013 See the whole document.	1-26
A	US 2008-0085836 A1 (KEARNS et al.) 10 April 2008 See the whole document.	1-26
A	MUNNE, 'Preimplantation genetic diagnosis for aneuploidy and translocations using array comparative genomic hybridization' Current Genomics, Vol.13, No.6, pp.463-470 (2012) See the whole document.	1-26

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 December 2015 (23.12.2015)	**23 December 2015 (23.12.2015)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
KIM, Seung Beom
Telephone No. +82-42-481-3371

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/056037

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014-0206552 A1	24/07/2014	None	
US 2012-0270212 A1	25/10/2012	AU 2011-358564 A1	05/09/2013
		AU 2011-358564 A2	12/09/2013
		AU 2012-385961 A1	30/01/2014
		CA 2774252 A1	07/04/2011
		CA 2798758 A1	24/11/2011
		CA 2821906 A1	28/06/2012
		CA 2824387 A1	16/08/2012
		CA 2877493 A1	30/01/2014
		CN 102597266 A	18/07/2012
		CN 103608466 A	26/02/2014
		CN 103608818 A	26/02/2014
		CN 104685064 A	03/06/2015
		EP 2473638 A1	11/07/2012
		EP 2572003 A1	27/03/2013
		EP 2656263 A2	30/10/2013
		EP 2673729 A1	18/12/2013
		EP 2847347 A1	18/03/2015
		EP 2854056 A2	01/04/2015
		EP 2854056 A3	03/06/2015
		EP 2854057 A2	01/04/2015
		EP 2854057 A3	26/08/2015
		EP 2854058 A2	01/04/2015
		EP 2885445 A1	24/06/2015
		EP 2902500 A1	05/08/2015
		IL 227842 D0	30/09/2013
		JP 2014-502845 A	06/02/2014
		JP 2014-507141 A	27/03/2014
		JP 2015-526073 A	10/09/2015
		KR 10-2015-0038216 A	08/04/2015
		RU 2013-141237 A	20/03/2015
		US 2011-0288780 A1	24/11/2011
		US 2012-0122701 A1	17/05/2012
		US 2012-0185176 A1	19/07/2012
		US 2013-0123120 A1	16/05/2013
		US 2013-0196862 A1	01/08/2013
		US 2013-178373 A1	11/07/2013
		US 2015-051087 A1	19/02/2015
		US 8825412 B2	02/09/2014
		US 9163282 B2	20/10/2015
		WO 2011-041485 A1	07/04/2011
		WO 2011-146632 A1	24/11/2011
		WO 2012-088456 A2	28/06/2012
		WO 2012-108920 A1	16/08/2012
		WO 2013-052557 A2	11/04/2013
		WO 2013-052557 A3	20/06/2013
		WO 2013-130848 A1	06/09/2013
		WO 2014-018080 A1	30/01/2014

Petitioner Illumina, Inc., EX1003, p. 653

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2015/056037

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2014-028778 A1	20/02/2014
US 2013-0288242 A1	31/10/2013	US 2008-0050739 A1	28/02/2008
		US 2009-0280492 A1	12/11/2009
		US 2010-0291571 A1	18/11/2010
		US 2011-0171638 A1	14/07/2011
		US 2012-0183963 A1	19/07/2012
		US 2013-0280709 A1	24/10/2013
US 2008-0085836 A1	10/04/2008	None	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**23 December 2015 (23.12.2015)**
Applicant's or agent's file reference GSGE-029/01WO 29258/146	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2015/056037	**16 October 2015 (16.10.2015)**	17 October 2014 (17.10.2014)

International Patent Classification (IPC) or both national classification and IPC

C12Q 1/68(2006.01)i, G06F 19/20(2011.01)i

Applicant

GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea Facsimile No. +82-42-472-7140	23 December 2015 (23.12.2015)	KIM, Seung Beom Telephone No. +82-42-481-3371

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/056037

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:
      ☐ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/056037

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	12-13,26	YES
	Claims	1-11,14-25	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-26	NO
Industrial applicability (IA)	Claims	1-26	YES
	Claims	NONE	NO

2. Citations and explanations :

※ NOTE: The written opinion has been established as if claim 26 had referred to claim 18 instead of claim 1.

Reference is made to the following document:
D1: US 2014-0206552 A1 (NATERA, INC.) 24 July 2014

1. Novelty and Inventive Step

1.1. Claims 1-17

1.1.1. Independent Claim 1

Claim 1 relates to a method for determining ploidy of an embryo, the method comprising:
(a) amplifying, using a primer pair that amplifies a plurality of human genomic loci, nucleic acid from a preimplantation embryo to generate a plurality of amplicons;
(b) sequencing the amplicons to generate a plurality of sequence reads;
(c) matching the sequence reads to the genomic loci and counting a number of matches; and
(d) determining chromosome count based on the number of matches.

D1, which is considered to be the closest prior art to the subject matter of claim 1, discloses a method for determining a ploidy state of an embryo at a chromosome of interest, the method comprising:
(a') obtaining a genetic sample from the embryo and preparing the genetic sample for sequencing, wherein the preparing step comprises preferentially enriching the DNA in the genetic sample at a plurality of polymorphic loci by performing targeted PCR amplification of the DNA;

Continued on Supplemental Box

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/056037

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 relates to a method, but claim 26 dependent on claim 1 relates to a system. As claim 26 does not clearly define the matter for which protection is sought, this claim does not meet the requirement of PCT Article 6.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Box No. V

(b') sequencing the genetic sample to give sequencing data;
(c') counting the number of sequence reads in the sequence data associated with each of the plurality of loci on the chromosome of interest; and
(d') determining the most likely ploidy state of the chromosome of interest given the sequence read count associated with each allele (see claims 1, 6-7).

D1 also discloses that in the targeted PCR, forward and reverse primers anneal the same fragment to enable amplification, and the method of D1 is used for preimplantation genetic diagnosis (see paragraphs [0002], [0151]). Accordingly, claim 1 is substantially the same as D1.

Therefore, claim 1 lacks novelty under PCT Article 33(2) and does not involve an inventive step under PCT Article 33(3).

1.1.2. Dependent Claims 2-11, 14-17

Concerning the additional features of claims 2-7, D1 discloses the step of obtaining the genetic sample from the embryo, wherein the genetic sample is one to five cells biopsied from the embryo, and also discloses a trophectoderm biopsy (see claims 1-2; and paragraph [0230]).

Concerning the additional features of claims 8-11, D1 discloses a multiplex pool of PCR assays designed to amplify SNP loci on chromosomes X, Y, 13, 18 and 21 (see paragraph [0171]). D1 also discloses that targeted PCR targets a plurality of loci on the chromosome of interest and on one or more reference chromosomes, wherein the reference chromosomes are assumed to be disomic (see paragraphs [0022], [0045]).

Concerning the additional features of claims 14-16, D1 discloses that sequencing adapters with barcodes are added to the PCR products, and that a second round of PCR is used to amplify the sequences with universal primer sequences (see paragraphs [0148], [0234]).

Concerning the additional feature of claim 17, D1 discloses that the DNA is highly fragmented (see paragraph [0151]).

Consequently, claims 2-11 and 14-17 lack novelty under PCT Article 33(2) and do not involve an inventive step under PCT Article 33(3).

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1.1.3. Dependent Claims 12-13

The additional feature of claim 12 defines the determining step as comprising the generation and comparison of a z-score for a chromosome of interest, rendering this claim different from D1. However, the z-score in chromosome count can be easily derived by a person skilled in the art within technical common sense.

The additional feature of claim 13 further comprises determining a euploidy or aneuploidy state of the embryo based on the chromosome count, rendering this claim different from D1. However, D1 discloses that the method of D1 can detect possible ploidy states comprising aneuploidy and euploidy (see abstract; and paragraph [0222]). Accordingly, claim 13 would have been obvious in view of D1.

Consequently, claims 12-13 are considered to be novel under PCT Article 33(2), but do not involve an inventive step under PCT Article 33(3).

1.2. Claims 18-26

1.2.1. Independent Claim 18

Claim 18 relates to a system for determining chromosome count, the system comprising a processor coupled to a tangible memory subsystem storing instructions that when executed by the processor cause the system to:
(a) obtain sequence reads from amplicons, wherein the amplicons are generated by amplifying, using a primer pair that amplifies a plurality of human genomic loci, nucleic acid from a preimplantation embryo;
(b) match the sequence reads to the genomic loci;
(c) count a number of matches at the genomic loci; and
(d) determine chromosome count based on the number of matches.

As described in point 1.1, D1 discloses the method for determining a ploidy state of the embryo comprising steps corresponding to the steps (a)-(d) of claim 18. D1 also discloses a computer program product tangibly embodied in a machine-readable storage device for execution by a programmable processor, and method steps of D1 can be performed by the programmable processor executing a program of instructions to perform functions by operating on input data and generating output (see paragraph [0128]). Accordingly, claim 18 is

Continued on The Next Page

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Previous Page

substantially the same as D1.

Therefore, claim 18 lacks novelty under PCT Article 33(2) and does not involve an inventive step under PCT Article 33(3).

1.2.2. Dependent Claims 19-25

The additional features of claims 19-25 correspond to the features of claims 2-4, 7-8 and 10-11, respectively. Accordingly, as reviewed under points 1.1.2 and 1.2.1, claims 19-25 are substantially the same as D1.

Consequently, claims 19-25 lack novelty under PCT Article 33(2) and do not involve an inventive step under PCT Article 33(3).

1.2.3. Dependent Claim 26

The additional feature of claim 26 defines the instructions as causing the system to determine and report a euploidy or aneuploidy state of the embryo based on the chromosome count, rendering this claim different from D1.

However, as described in point 1.1.3, D1 discloses that the method of D1 can detect possible ploidy states comprising aneuploidy and euploidy. Accordingly, claim 26 would have been obvious in view of D1.

Therefore, claim 26 is considered to be novel under PCT Article 33(2), but does not involve an inventive step under PCT Article 33(3).

2. Industrial Applicability

Claims 1-26 are industrially applicable under PCT Article 33(4).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

ENTERED IN CPI

PCT

To: Thomas C. Meyers
Brown Rudnick LLP
One Financial Center
Boston, MA 02111
United States of America

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 29 JAN 2015
Applicant's or agent's file reference GSGE-020/01WO 29258/108	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US14/61138	International filing date *(day/month/year)* 17 October 2014 (17.10.2014)
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

29 JAN 2015

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-020/01WO 29258/108	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US14/61138	International filing date *(day/month/year)* 17 October 2014 (17.10.2014)	(Earliest) Priority Date *(day/month/year)* 18 October 2013 (18.10.2013)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☐ as suggested by the applicant.
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

Petitioner Illumina, Inc., EX1003, p. 664

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/61138

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2014.01)
CPC - C12Q 1/6874, 1/68
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07H 21/04; C12P 19/34; C12Q 1/68 (2014.01)
CPC: C07D 471/04, 401/06, 487/04, 337/08, 409/04, 213/04; C12Q 1/68, 1/6874; USPC: 536/24.3, 23.1, 22.1, 18.7, 1.11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); PubMed; ScienceDirect; Google Scholar; 'SMN1,' exon, intron, 'rs212214,' ' rs212213,' 'spinal muscular atrophy,' carrier

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y — A	UMBARGER, M et al. Next-Generation Carrier Screening. Genetics in Medicine. 13 June 2013; Vol. 16, No. 2; pages 132-140; abstract; page 132, right column, second paragraph; page 134, left column, second paragraph; page 134, right column, fourth paragraph to page 135, right column, first paragraph; page 136, left column, third paragraph; page 136, figure 2d. DOI:10.1038/gim.2013.83.	1, 6, 7 — 2-4, 8-10 — 5
Y — A	WO 2012/170725 A2 (MOUNT SINAI SCHOOL OF MEDICINE) December 13, 2012; abstract; paragraphs [0002], [0003], [0008]	2-4, 8-10 — 5
Y — A	WO 2011/06020 A1 (GENZYME CORPORATION) May 19, 2011; paragraphs [0005], [0006], [0074]	8-10 — 5

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2015 (13.01.2015)	29 JAN 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

29 JAN 2015

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Thomas C. Meyers
Brown Rudnick LLP
One Financial Center
Boston, MA 02111
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	29 JAN 2015

Applicant's or agent's file reference	FOR FURTHER ACTION
GSGE-020/01WO 29258/108	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US14/61138	17 October 2014 (17.10.2014)	18 October 2013 (18.10.2013)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2014.01)
CPC - C12Q 1/6874, 1/68

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	13 January 2015 (13.01.2015)	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

29 JAN 2015

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/61138

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/61138

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-10	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	5	YES
	Claims	1-4, 6-10	NO
Industrial applicability (IA)	Claims	1-10	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 6 and 7 lack an inventive step under PCT Article 33(3) as being obvious over the publication entitled 'Next-Generation Carrier Screening' by Umbarger, et al. (hereinafter 'Umbarger').

As per claim 1, Umbarger discloses a method for determining carrier status of an autosomal recessive disease (a method for carrier screening for recessive disorders (autosomal recessive disease); recessive Mendelian disorder; abstract), the method comprising the steps of: capturing (page 132, right column, second paragraph), using non-naturally occurring synthesized molecular inversion probes ((non-naturally occurring) synthetic molecular inversion probe; page 132, right column, second paragraph; page 134, left column, third paragraph), nucleic acid (genomic DNA was subjected to target capture using probes; page 134, left column, second paragraph) corresponding to at least one genomic locus that is linked to a genomic locus that is diagnostic for an autosomal recessive disease (sequencing for genomic mutations associated with a carrier of a recessive disorder; abstract; page 134, right column, fourth paragraph to page 135, right column, first paragraph); sequencing, using a sequencing instrument, said captured nucleic acid (sequencing of a captured genomic DNA product using Illumina HiSeq 2000; page 134, left column, second paragraph); determining copy number of said captured nucleic acid (a variation in copy number was seen in samples; page 134, left column, second paragraph; page 136, left column, third paragraph; page 136, figure 2d). Umbarger does not disclose determining disease status based upon said copy number. However, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have understood that the disease status can be readily determined by copy number, provided the previously disclosed determination of copy number (Umbarger; page 136, left column, third paragraph; page 136, figure 2d), and the previous disclosure of a method for determining disease carrier status based on genetic approaches (Umbarger; abstract), through routine experimentation and testing in a laboratory, for implementing an accurate test for determining disease carrier status of an individual based on gene copy number.

As per claim 6, Umbarger discloses the method of claim 1, and Umbarger further discloses wherein said sequencing step comprises a Sanger sequencing method (Sanger sequencing; abstract) or a next-generation sequencing method.

As per claim 7, Umbarger discloses the method of claim 1, and Umbarger further discloses wherein said capturing step comprises isolating said nucleic acid from a sample comprising nucleic acid from a subject (capture of genes from genomic DNA isolated from whole blood (wherein said capturing step comprises isolating said nucleic acid from a sample comprising nucleic acid from a subject); abstract).

Claims 2-4 lack an inventive step under PCT Article 33(3) as being obvious over Umbarger in view of WO 2012/170725 A2 (MOUNT SINAI SCHOOL OF MEDICINE) (hereinafter 'Mount Sinai').

As per claim 2, Umbarger discloses the method of claim 1, and Umbarger further discloses detecting an autosomal recessive disease (recessive Mendelian disorder (autosomal recessive disorder); abstract). Umbarger does not disclose wherein said autosomal recessive disease is spinal muscular atrophy. Mount Sinai discloses detecting spinal muscular atrophy (spinal muscular atrophy; abstract). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of determining disease carrier status, as previously disclosed by Umbarger, with detecting spinal muscular atrophy, as previously disclosed by Mount Sinai, as the previous disclosure by Umbarger includes a method for determining the genetic status of genes associated with a recessive disorder (Umbarger; abstract), Mount Sinai discloses detecting spinal muscular atrophy, which is an autosomal recessive disorder (Mount Sinai; paragraph [0002]), and a combination of these references would have resulted in a superior method for determining the genetic carrier status for spinal muscular atrophy in an individual.

-***-Continued on Next Supplemental Page-***-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/61138

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V:
-Continued from Citations and Explanations:

As per claim 3, Umbarger and Mount Sinai, in combination, disclose the method of claim 2, and Umbarger further discloses detecting a genomic locus (genomic loci; page 136, left column, first paragraph). Umbarger does not disclose wherein said at least one genomic locus is on intron 7 of an SMN1 or SMN2 gene or both. Mount Sinai discloses wherein said at least one genomic locus is on intron 7 of an SMN1 (g.27134T>G from SMN intron 7 (wherein at least one genomic locus is on intron 7 of an SMN1 gene; paragraph [0008]) or SMN2 gene or both, where SMN1 mutations are associated with spinal muscular atrophy carrier status (Mount Sinai; paragraph [0003]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of determining disease carrier status, as previously disclosed by Umbarger, with a genomic locus in intron 7 of an SMN1 gene, as previously disclosed by Mount Sinai, as the previous disclosure by Umbarger includes a method for determining the genetic status of genes associated with a recessive disorder (Umbarger; abstract), Mount Sinai discloses that spinal muscular atrophy is an autosomal recessive disorder (Mount Sinai; paragraph [0002]), and that SMN1 mutations are associated with spinal muscular atrophy carrier status (Mount Sinai; paragraph [0003]), and a combination of these references would have resulted in a superior method for determining the genetic carrier status for spinal muscular atrophy in an individual.

As per claim 4, Umbarger and Mount Sinai, in combination, disclose the method of claim 3, and Umbarger further discloses the detection of an autosomal recessive disease (recessive Mendelian disorder (autosomal recessive disorder); abstract), and a genomic locus (genomic loci; page 136, left column, first paragraph). Umbarger does not disclose wherein said genomic locus that is diagnostic for an autosomal recessive disease is on exon 7 of an SMN1 gene (in SMA patients, SMN1 exon 7 and 8 are rendered non-functional (wherein said genomic locus that is diagnostic for an autosomal recessive disease is on exon 7 of an SMN1 gene); paragraph [0003]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of determining disease carrier status, as previously disclosed by Umbarger, with a genomic locus in exon 7 of an SMN1 gene, as previously disclosed by Mount Sinai, as the previous disclosure by Umbarger includes a method for determining the genetic status of genes associated with a recessive disorder (Umbarger; abstract), Mount Sinai discloses that spinal muscular atrophy is an autosomal recessive disorder (Mount Sinai; paragraph [0002]), and that SMN1 mutations are associated with spinal muscular atrophy carrier status (Mount Sinai; paragraph [0003]), and a combination of these references would have resulted in a superior method for determining the genetic carrier status for spinal muscular atrophy in an individual.

Claims 8-10 lack an inventive step under PCT Article 33(3) as being obvious over Umbarger and Mount Sinai and further in view of WO 2011/060240 A1 (GENZYME CORPORATION) (hereinafter 'Genzyme').

As per claim 8, Umbarger and Mount Sinai, in combination, disclose the method of claim 7, and Umbarger further discloses analyzing a blood sample (whole blood; abstract). Umbarger does not disclose wherein said sample is a maternal blood sample. Genzyme discloses a method for using a gene copy number to determine a disease status of a fetus (paragraph [0074]), wherein said sample is a maternal blood sample (maternal blood (sample); paragraph [0074]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of determining the genetic status of a sample, as previously disclosed by Umbarger, through use of a maternal blood sample, as previously disclosed by Genyzme, as the previous disclosure by Umbarger includes a method for genetically determining carrier status of a disease in a blood sample using next-generation sequencing methods (Umbarger; abstract), Genzyme discloses a method for using gene copy number to determine disease status of a fetus using a maternal blood sample (Genzyme; paragraph [0074]), and a combination of these references would have resulted in a superior method for using next-generation sequencing methods to determine disease status using a maternal blood sample.

As per claim 9, Umbarger, Mount Sinai and Genyzme, in combination, disclose the method of claim 8, and Umbarger further discloses analyzing a blood sample (whole blood; abstract). Umbarger does not disclose wherein said maternal blood sample comprises cell free circulating nucleic acid. Genzyme discloses a method for using a gene copy number to determine a disease status of a fetus (paragraph [0074]), wherein said maternal blood sample comprises cell free circulating nucleic acid (a maternal blood sample which comprises cell-free maternal and fetal (circulating) nucleic acids; paragraph [0074]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of determining the genetic status of a sample, as previously disclosed by Umbarger, with a maternal blood sample comprising cell-free circulating nucleic acids, as previously disclosed by Genzyme, as the previous disclosure by Umbarger includes a method for genetically determining carrier status of a disease in nucleic acids isolated from a blood sample using next-generation sequencing methods (Umbarger; abstract), Genzyme discloses a method for using gene copy number to determine disease status of a fetus using a maternal blood sample comprising cell-free nucleic acids (Genzyme; paragraph [0074]), and a combination of these references would have resulted in a superior method for using next-generation sequencing methods to determine disease status using cell-free nucleic acids obtained from a maternal blood sample.

As per claim 10, Umbarger, Mount Sinai and Genzyme, in combination, disclose the method of claim 9, and Umbarger further discloses the detection of an isolated nucleic acid (DNA (nucleic acid) isolated from whole blood; abstract). Umbarger does not disclose wherein at least a portion of the cell free circulating nucleic acid is from a fetus being carried within the subject. Genzyme discloses a method for using a gene copy number to determine a disease status of a fetus (paragraph [0074]), wherein at least a portion of the cell free circulating nucleic acid is from a fetus being carried within the subject (a maternal blood sample which comprises cell-free maternal and fetal (circulating) nucleic acids taken from a pregnant woman; paragraph [0074]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have combined the method of determining the genetic status of a sample, as previously disclosed by Umbarger, with a maternal blood sample comprising cell-free fetal circulating nucleic acids, as previously disclosed by Genzyme, as the previous disclosure by Umbarger includes a method for genetically determining carrier status of a disease in nucleic acids isolated from a blood sample using next-generation sequencing methods (Umbarger; abstract), Genzyme discloses a method for using a gene copy number to determine a disease status of a fetus using a maternal blood sample comprising fetal cell-free nucleic acids (Genzyme; paragraph [0074]), and a combination of these references would have resulted in a superior method for using next-generation sequencing methods for determining fetal disease status using cell-free nucleic acids obtained from a maternal blood sample.

-***-Continued on Next Supplemental Page-***-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/61138

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V:
-Continued from Citations and Explanations:

Claim 5 meets the criteria set-out in PCT Articles 33(2)-(3), because the prior art does not teach or fairly suggest the method of claim 4, wherein said at least one genomic locus is selected from rs212214 and rs212213.

Umbarger discloses a method for determining carrier status of an autosomal recessive disease (a method for carrier screening for recessive disorders (autosomal recessive disease); recessive Mendelian disorder; abstract), the method comprising the steps of: capturing (capture; page 132, right column, second paragraph), using non-naturally occurring synthesized molecular inversion probes ((non-naturally occurring) synthetic molecular inversion probe; page 132, right column, second paragraph; page 143, left column, third paragraph), nucleic acid (genomic DNA was subjected to target capture using probes; page 134, left column, second paragraph) corresponding to at least one genomic locus that is linked to a genomic locus that is diagnostic for an autosomal recessive disease (sequencing for genomic mutations associated with a carrier of a recessive disorder (corresponding to at least one genomic locus that is linked to a genomic locus that is diagnostic for an autosomal recessive disease); abstract; page 134, right column, fourth paragraph to page 135, right column, first paragraph); sequencing, using a sequencing instrument, said captured nucleic acid (sequencing of a captured genomic DNA product using Illumina HiSeq 2000; page 134, left column, second paragraph); determining copy number of said captured nucleic acid (a variation in copy number was seen in samples; page 134, left column, second paragraph; page 136, left column, third paragraph; page 136, figure 2d). Umbarger does not disclose wherein said at least one genomic locus is selected from rs212214 and rs212213.

Mount Sinai discloses a genomic locus on intron 7 of an SMN1 (g.27134T>G from SMN intron 7 (wherein at least one genomic locus is on intron 7 of an SMN1 gene); paragraph [0008]). Mount Sinai does not disclose wherein said at least one genomic locus is selected from rs212214 and rs212213.

Genzyme discloses determining copy number of target loci SMARCC1 and SUPT5H of SMN1 exon 7 (a method for analyzing a target locus, such as SMARCC1 and SUPT5H to determine gene copy number; paragraphs [0005], [0006]). Genzyme does not disclose the method of claim 4, wherein said at least one genomic locus is selected from rs212214 and rs212213.

The prior art does not teach or fairly suggest the method of claim 4, wherein the genomic locus is selected from rs212214 and rs212213, and sufficient motivation, based upon the previous disclosures of the Umbarger, Mount Sinai and Genzyme references does not exist to have integrated a genomic locus selected from rs212214 and rs212213 on an SMN1 gene.

Claims 1-10 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-007/01WO29258/52	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 13/33435	International filing date *(day/month/year)* 22 March 2013 (22.03.2013)	(Earliest) Priority Date *(day/month/year)* 04 April 2012 (04.04.2012)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 13/33435

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G06F 19/22 (2013.01)
USPC - 702/19, 20
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - G06F 19/22 (2013.01)
USPC - 702/19, 20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB,USPT,USOC,EPAB,JPAB); PubMed (MEDLINE);
Search terms: contig, reads, alignment, insertion, deletion, mutation, reference, reference, mutation, polymorphism, SNP, identify, determine, assay, evaluate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ------ Y	US 2011/0257889 A1 (KLAMMER et al.) 20 October 2011 (20.10.2011) para [0003], [0014], [0016], [0040], [0041], [0043], [0049], [0050], [0061], [0073], [0085], [0086], [0083]	1-6, 9-12 ---------- 7-8
Y	US 2009/0192047 A1 (PARR et al.) 30 July 2009 (30.07.2009) para [0236]; Table 4	7-8
X,P	US 8,209,130 B1 (KENNEDY et al.) 26 June 2012 (26.06.2012) entire document	1-12
A	KLEIN et al., LOCAS--a low coverage assembly tool for resequencing projects. PLoS One; 2011 (published online 15 August 2011); Vol 6, No 8, Document e23455; entire document	1-12
A	US 2004/0152108 A1 (KEITH et al.) 5 August 2004 (05.08.2004) entire document	1-12
A	US 2004/0142325 A1 (MINTZ et al.) 22 July 2004 (22.07.2004) entire document	1-12

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 May 2013 (03.05.2013)	10 JUN 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	10 JUN 2013

Applicant's or agent's file reference	FOR FURTHER ACTION
GSGE-007/01WO29258/52	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 13/33435	22 March 2013 (22.03.2013)	04 April 2012 (04.04.2012)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G06F 19/22 (2013.01)
USPC - 702/19, 20

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to th IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	03 May 2013 (03.05.2013)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/33435

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account **the rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRIT. OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

Inter nal application No.
PCT/US 13/33435

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	7-9	YES
	Claims	1-6, 10-12	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-6 and 10-12 lack novelty under PCT Article 33(2) as being anticipated by US 2011/0257889 A1 to Klammer et al. (hereinafter 'Klammer').

Regarding claim 1, Klammer discloses a method for identifying a mutation in a nucleic acid, the method comprising: sequencing nucleic acid to generate a plurality of sequence reads (para [0049]); creating a contig based on the reads (para [0016], [0040], [0050]); aligning the contig to a reference sequence (para [0017], [0043]); aligning the individual reads back to the contig (para [0050]); and identifying a mutation based on the alignments to the contig and the reference sequence (para [0043] - mutation that distinguishes the nucleotide sequence of the reference sequence).

Regarding claim 2, Klammer discloses wherein the method of claim 1 may further comprise splitting the reads into subsets corresponding to known locations (para [0083] - "overlap detection algorithms described above generally require a "query" and a "target," and so for de novo sequencing the sequence read dataset must provide both. In FIG. 5, the sequence dataset is provided to the algorithm as a plurality of subsets of the input sequence data set ("split data"), and these subsets can be used as the "query" or the "target" in a single pairwise comparison. In certain preferred embodiments, multiple of the subsets are combined to form a larger target for the comparison"; para [0086] - identifying locations of alignments between multiple occurrences of a known sequence within the sequencing read).

Regarding claim 3, Klammer discloses wherein the method of claim 1 may further comprise identifying a mutation in the contig relative to the reference (para [0043] - "loci that have basecalls that differ from the reference sequence can be further analyzed to determine if a given locus was erroneously called in the sequence read, or if it represents a true variation (e.g., a mutation, SNP variant, etc.)").

Regarding claim 4, Klammer discloses wherein the method of claim 1 may further comprise determining a position of the mutation in the nucleic acid based on a position of the mutation in the reads and the alignments to the contig and the reference sequence (para [0043] - "methods for aligning and assembling sequence reads based at least in part on a known reference sequence, which is sometimes termed "resequencing" or "mapping." In such embodiments, the sequence reads can be mapped to the reference sequence, and loci that have basecalls that differ from the reference sequence can be further analyzed to determine if a given locus was erroneously called in the sequence read, or if it represents a true variation (e.g., a mutation, SNP variant, etc.)"; para [0061]; the fourth position is mutated).

Regarding claim 5, Klammer discloses wherein the method of claim 1 may further comprise wherein the mutation may be selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, a substitution, and a translocation (para [0041], [0043]).

Regarding claim 6, further to the method of claim 1, Klammer discloses wherein a plurality of mutations may be identified (para [0014] - multiple deletion or insertions).

Regarding claim 10, further to the method of claim 1, Klammer discloses wherein the mutation may be associated with a disease (para [0003], [0004]).

Regarding claim 11, further to the method according to claim 1, Klammer discloss wherein sequencing may be sequencing-by-synthesis (para [0065]).

Regarding claim 12, further to the method according to claim 11, Klammer discloses wherein sequencing-by-synthesis may be a single molecule sequencing-by-synthesis (para [0036] - single-molecule real-time (SMRT.TM.) sequencing).

- Please see Supplemental Box for continuation -

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 13/33435

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box V.2: Citations and Explanations

Claim 9 lacks an inventive step under PCT Article 33(3) as being obvious over Klammer, as above.

Regarding claim 9, although Klammer does not expressly recite wherein the mutation is a deletion at an end of a sequence read, Klammer discloses wherein the mutation may be a deletion (para [0073]; k-mer ATGC may contain missing base, thereby producing deletion ATG). It would have been obvious to a person of ordinary skill in the art to anticipate wherein a mutation or errant base call may have been made at the end of a sequence read, or in a gap between sequence reads, due to a known tendency of polymerases to add bases beyond the end of a template, based on both the nucleotide mix available, and the preferences inherent in the particular polymerase.

Claims 7-8 lack inventive step under PCT Article 33(3) as being obvious over Klammer, as above, in view of US 2009/0192047 A1 to Parr et al. (hereinafter 'Parr').

Regarding claims 7-8, further to the method of claim 6, Klammer does not specifically teach the further limitations taught by Parr, wherein a first mutation may be within about 100 nucleotides of a second mutation, and wherein the first mutation may be a substitution and the second mutation may be a deletion (para [0236], Table 4). As Klammer further teaches wherein nucleotide sequence mutations may encompass multiple adjacent positions in the reference and/or sequencing reads (para [0043]), it would have been obvious to one having ordinary skill in the art that the method of claim 6 might further comprise wherein a first mutation may be within about 100 nucleotides of a second mutation, and wherein the first mutation may be a substitution and the second mutation may be a deletion, as taught by Parr.

Claims 1-12 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

39958/138

From the INTERNATIONAL SEARCHING AUTHORITY

ENTER PCT IN CPI

To:
Meyers, Thomas C.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference GSGE-023/01WO 2925	Date of mailing *(day/month/year)* 2 December 2015 (02-12-2015) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2015/049132	International filing date *(day/month/year)* 9 September 2015 (09-09-2015)
Applicant GOOD START GENETICS, INC.	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   How? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis* 1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer WEZYK, Magdalena Tel: +49 (0)89 2399-8315

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
GSGE-023/01WO 2925		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2015/049132	9 September 2015 (09-09-2015)	10 September 2014 (10-09-2014)
Applicant		
GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 2
      [ ] as suggested by the applicant
      [X] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/049132

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S. J. GREEN ET AL: "Suicide Polymerase Endonuclease Restriction, a Novel Technique for Enhancing PCR Amplification of Minor DNA Templates", APPLIED AND ENVIRONMENTAL MICROBIOLOGY, vol. 71, no. 8, 1 August 2005 (2005-08-01) , pages 4721-4727, XP055229646, US ISSN: 0099-2240, DOI: 10.1128/AEM.71.8.4721-4727.2005	1-12, 16-18
Y	p. 4721, right-hand col., last para.; p. 4723, right-hand col., last para. - p. 4724, right-hand col., 1st para.; fig. 1, 2	13-15
	----- -/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2015	02/12/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ripaud, Leslie

1

Form PCT/ISA/210 (second sheet) (April 2005)

Petitioner Illumina, Inc., EX1003, p. 681

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/049132

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STUART K ARCHER ET AL: "Selective and flexible depletion of problematic sequences from RNA-seq libraries at the cDNA stage", BMC GENOMICS, BIOMED CENTRAL LTD, LONDON, UK, vol. 15, no. 1, 26 May 2014 (2014-05-26), page 401, XP021187323, ISSN: 1471-2164, DOI: 10.1186/1471-2164-15-401	1,2, 7-11,16, 17
Y	p. 2, para. bridging left- to right-hand col.; p. 3, left-hand col., last para. - right-hand col., last para.; fig. 1	13-15

X	US 2005/003369 A1 (CHRISTIANS FREDERICK C [US] ET AL) 6 January 2005 (2005-01-06)	1,2, 7-11, 16-18
Y	para. 5-8, 47, 51-55; fig. 1A	13-15

X	WO 2013/191775 A2 (NUGEN TECHNOLOGIES INC [US]; ARMOUR CHRISTOPHER [US]; AMORESE DOUG [US) 27 December 2013 (2013-12-27) cited in the application	1-12, 16-18
Y	para. 5, 6, 12, 202; fig. 1	13-15

Y	PORRECA GREGORY J ET AL: "Multiplex amplification of large sets of human exons", NATURE METHODS, NATURE PUBLISHING GROUP, GB, vol. 4, no. 11, 1 November 2007 (2007-11-01), pages 931-936, XP002525088, ISSN: 1548-7091, DOI: 10.1038/NMETH1110 cited in the application abstract; fig. 1	13-15

X,P	WO 2015/119941 A2 (IGENOMX INTERNAT GENOMICS CORP [US]) 13 August 2015 (2015-08-13) the whole document	1-18

A	DONNA J. E. HOUSLEY ET AL: "SNP Discovery and Haplotype Analysis in the Segmentally Duplicated DRD5 Coding Region", ANNALS OF HUMAN GENETICS, vol. 73, no. 3, 1 May 2009 (2009-05-01), pages 274-282, XP055230245, GB ISSN: 0003-4800, DOI: 10.1111/j.1469-1809.2009.00513.x abstract	1-18

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

Petitioner Illumina, Inc., EX1003, p. 682

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/049132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005003369 A1	06-01-2005	US 2005003369 A1	06-01-2005
		US 2005123987 A1	09-06-2005
WO 2013191775 A2	27-12-2013	CA 2877094 A1	27-12-2013
		CN 104619894 A	13-05-2015
		EP 2861787 A2	22-04-2015
		GB 2518078 A	11-03-2015
		JP 2015521468 A	30-07-2015
		US 2015299767 A1	22-10-2015
		WO 2013191775 A2	27-12-2013
WO 2015119941 A2	13-08-2015	NONE	

Form PCT/ISA/210 (patent family annex) (April 2005)

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
PCT/US2015/049132

TITLE: METHODS FOR SELECTIVELY SUPPRESSING NON-TARGET SEQUENCES

APPLICANT: GOOD START GENETICS, INC.

IPC CLASSIFICATION: C12Q1/68

EXAMINER: Ripaud, Leslie

CONSULTED DATABASES: NPL, BIOSIS, DOSYS, EMBASE, EPODOC, FSTA, INET, MEDLINE, WPI, XFULL, XPESP, XPSPRNG

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: 1- C12Q1/6806,C12Q2521/301,C12Q2533/101,C12Q2537/159, C12Q1/6806

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
Method of removing unwanted (non-target) sequences from a population of nucleic acids comprising hybridising an oligonucleotide to the unwanted sequence and digesting the double-stranded region formed. In some embodiments the oligonucleotide is extended prior to cleavage. Cleavage by endonuclease.

EPO FORM P04A42

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2015/049132	09.09.2015	10.09.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C12Q1/68

Applicant
GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Ripaud, Leslie Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/049132

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Petitioner Illumina, Inc., EX1003, p. 686

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13-16
	No:	Claims	1-12, 17, 18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Cited documents

Reference is made to the following documents:

D1 S. J. GREEN ET AL: "Suicide Polymerase Endonuclease Restriction, a Novel Technique for Enhancing PCR Amplification of Minor DNA Templates",
APPLIED AND ENVIRONMENTAL MICROBIOLOGY,
vol. 71, no. 8, 1 August 2005 (2005-08-01), pages 4721-4727, XP055229646,
ISSN: 0099-2240, DOI: 10.1128/AEM.71.8.4721-4727.2005

D2 STUART K ARCHER ET AL: "Selective and flexible depletion of problematic sequences from RNA-seq libraries at the cDNA stage",
BMC GENOMICS,
vol. 15, no. 1, 26 May 2014 (2014-05-26), page 401, XP021187323,
ISSN: 1471-2164, DOI: 10.1186/1471-2164-15-401

D3 US 2005/003369 A1 (CHRISTIANS FREDERICK C [US] ET AL) 6 January 2005 (2005-01-06)

D4 WO 2013/191775 A2 (NUGEN TECHNOLOGIES INC [US]; ARMOUR CHRISTOPHER [US]; AMORESE DOUG [US) 27 December 2013 (2013-12-27)cited in the application

D5 PORRECA GREGORY J ET AL: "Multiplex amplification of large sets of human exons",
NATURE METHODS,
vol. 4, no. 11, 1 November 2007 (2007-11-01), pages 931-936, XP002525088,
ISSN: 1548-7091, DOI: 10.1038/NMETH1110
cited in the application

D6 WO 2015/119941 A2 (IGENOMX INTERNAT GENOMICS CORP [US]) 13 August 2015 (2015-08-13)

2 Novelty (A. 33(2) PCT)

2.1 The present application does not meet the criteria of A. 33(1) PCT, because the subject-matter of claims 1-12 and 17-18 is not new in the sense of A. 33(2) PCT.

Petitioner Illumina, Inc., EX1003, p. 688

2.2 D1 teaches a method of removing unwanted segments of a nucleic acid sample comprising (p. 4721, right-hand col., last para.; fig. 1, 2):

- extracting genomic DNA from a sample and denaturing it by heating so as to obtain single-stranded nucleic acids that contain unwanted segments (p. 4723, right-hand col., last para. - p. 4724, right-hand col., 1st para.; fig. 1; fig. 2, step 1),
- adding two complementary oligonucleotides that bind to sequences that flank unwanted regions so as to create double-stranded regions that contain part of the unwanted regions (p. 4721, right-hand col., last para.; fig. 1; fig. 2, steps 2 and 3),
- extend these oligonucleotides using a DNA polymerase to create extended double-stranded regions that contain the unwanted segments (p. 4721, right-hand col., last para.; fig. 1; fig. 2, steps 2 and 3),
- digesting the double-stranded regions with a restriction endonuclease, thereby removing the unwanted segments from the nucleic acid (p. 4721, right-hand col., last para.; fig. 1; fig. 2, step 4),
- deactivating the endonuclease (fig. 1), and
- analysing the remaining intact nucleic acids by PCR (p. 4724, para. bridging left- to right-hand col.).

This is prejudicial to the novelty of claims 1-12, 17 and 18.

2.3 D2 teaches a method of removing unwanted segments from a nucleic acid sample comprising (p. 2, para. bridging left- to right-hand col.; p. 3, left-hand col., last para. - right-hand col., last para.; fig. 1):

- generating a single-stranded cDNA sample containing wanted and unwanted segments,
- adding an oligonucleotide probe complementary to the unwanted segment so as to create a double-stranded region,
- digesting this double-stranded region using a duplex-specific nuclease,
- deactivating the enzyme by EDTA, and
- analysing the remaining intact nucleic acids by PCR and sequencing.

This is prejudicial to the novelty of claims 1, 2, 7-11 and 17.

2.4 D3 teaches a method of removing unwanted segments from a nucleic acid sample comprising (para. 5-8, 47, 51-55; fig. 1A):

Petitioner Illumina, Inc., EX1003, p. 689

- obtaining a population of single-stranded mRNAs containing wanted and unwanted sequences,
- adding an oligonucleotide probe complementary to the unwanted sequences so as to create a double-stranded region,
- digesting this double-stranded region using RNase H,
- deactivating the RNase H by heat, and
- amplifying the remaining intact nucleic acids.

This is prejudicial to the novelty of claims 1, 2, 7-11, 17 and 18.

2.5 D4 teaches a method of removing unwanted segments from a nucleic acid sample comprising (para. 5, 6, 12, 202; fig. 1):

- obtaining a population of single-stranded nucleic acids containing wanted and unwanted segments,
- adding a set of oligonucleotide primers complementary to the unwanted segments so as to create a double-stranded region,
- extending the primers with a polymerase so as to extend the double-stranded region,
- digesting this double-stranded region using a restriction endonuclease,
- deactivating the endonuclease by heat, and
- amplifying the remaining intact nucleic acids by PCR and analysing them by sequencing.

The starting sample is genomic DNA (para. 125).

D4 is prejudicial to the novelty of claims 1-12, 17 and 18.

3 Inventive Step (A. 33(3) PCT)

3.1 The present application does not meet the criteria of A.33(1) PCT, because the subject-matter of claims 13-16 does not involve an inventive step in the sense of A. 33(3) PCT.

3.2 D1 may be considered as closest prior art for claims 13-16 (see cited passages in para. 2.2 above). Claim 13 differs from D1 in that the assay comprises a step of capture by molecular inversion probes. The application does not provide data for the use of such probes. However, it appears that they can be used to further purify the sequences of interest. Therefore, the problem to be solved may be seen as further enriching the sample for the

sequences of interest. The use of molecular inversion probes to enrich a sample in sequences of interest was well-known in the art at the date of priority, as shown in D5 (abstract; fig. 1). Therefore, it would have been obvious to use such probes to solve the technical problem and claim 13 is not considered inventive in view of D1 and D5.

3.3 The additional features further characterising the method of claims 14 and 15 are disclosed in D5 (abstract). Hence, said claims lack an inventive step in view of D1 and D5.

3.4 Claim 16 pertains to routine modifications of the method of claim 1 which, in absence of a surprising effect, do not appear to render the method inventive. Hence, claim 16 lacks an inventive step in view of D1.

3.5 D2, D3 or D4 may as well be considered as closest prior art for claims 13-16 (see para. 2.3-2.5 above). It appears that said claims would also lack an inventive step in view of D2-D4, considered independently, for similar reasons as detailed above for D1 (see para. 3.2-3.4).

4 Industrial Applicability (A. 33(4) PCT)

4.1 The subject-matter of claims 1-18 is considered to be industrially applicable.

Re Item VI

Certain documents cited

1 The cited document D6 was published between the priority date and the date of filing of the present application. Therefore, it does not constitute prior art in PCT chapter II (R. 70(10) PCT). However, it could become relevant for novelty and inventive step in case the priority would prove to be invalid.

Re Item VIII

Certain observations on the international application

Petitioner Illumina, Inc., EX1003, p. 691

1 Claim 17 relates to a method including a step of "obtaining a sample from the subject". In view of the description (p. 5, l. 144), this may be performed by biopsy, which is considered as a surgical step, thereby rendering the whole method surgical and thus excluded from patentability (R. 39.1(iv) PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-026/01WO 29258/145	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 15/50964	International filing date *(day/month/year)* 18 September 2015 (18.09.2015)	(Earliest) Priority Date *(day/month/year)* 24 September 2014 (24.09.2014)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 8 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/50964

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 21/00; G01N 35/00; G01D 21/00; A61J 1/00 (2015.01)
CPC - G01N 33/84; G01N 21/29; G01K 11/12; A61J 1/18; A61J 1/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - G01N 21/00; G01N 35/00; G01D 21/00; A61J 1/00 (2015.01)
CPC - G01N 33/84; G01N 21/29; G01K 11/12; A61J 1/18; A61J 1/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Patents and non-patent literature (classification, keyword; search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar (NPL), Google Patents; search terms: biological sample, indicator, freez, pH, cell, contacting, visual, delivering, laboratory, position, dye, triarylmethane, phenol red, malachite green, lysing, nucleic acid, analyzing, alkaline lysis, neutralizing, embryonic, color change, eye, automatic, camera, electrical conductivity

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2012/0079980 A1 (TAYLOR et al.) 05 April 2012 (05.04.2012) para [0048], [0050], [0059], [0123], [0214]-[0215], [0412]-[0413], [0415]	1, 4-6, 8, 11-13 --- 2-3, 7, 9-10, 14
Y	US 2008/0176209 A1 (MULLER et al.) 24 July 2008 (24.07.2008) para [0002]-[0006], [0020], [0109], [0111], [0142], [0207], [0210]	2-3, 7, 9-10
Y	US 2009/0301382 A1 (PATEL) 10 December 2009 (10.12.2009) para [0051]-[0053], [0057], [0478], [0581]	14
A	US 8,778,609 B1 (UMBARGER) 15 July 2014 (15.07.2014) col 1, ln 13-14; col 2, ln 51-53, 64-67; col 3, ln 1-7, 16, 20-21, 63-65; col 4, ln 3-7; col 5, ln 2-5, 9-10; col 26, ln 56-60; col 27, ln 17-19	9
A	US 2002/0040216 A1 (DUMONT et al.) 04 April 2002 (04.04.2002) entire document	1-14

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 December 2015	22 JAN 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	22 JAN 2016

Applicant's or agent's file reference	FOR FURTHER ACTION
GSGE-026/01WO 29258/145	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 15/50964	18 September 2015 (18.09.2015)	24 September 2014 (24.09.2014)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G01N 21/00; G01N 35/00; G01D 21/00; A61J 1/00 (2015.01)
CPC - G01N 33/84; G01N 21/29; G01K 11/12; A61J 1/18; A61J 1/10

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule *43bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	29 December 2015	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 15/50964

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 15/50964

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-14	YES
	Claims	none	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1, 4-6, 8, and 11-13 lack an inventive step under PCT Article 33(3) as being obvious over US 2012/0079980 A1 to Taylor et al. (hereinafter "Taylor").

Regarding claim 1, Taylor teaches a method for processing a biological sample (para [0048], [0412]-[0413]), the method comprising: obtaining a sample comprising at least one cell in a solution (para [0412]-[0413]); and contacting the sample (para [0415]) with an indicator that provides a visual indication that the sample is frozen (para [0048], [0059], [0123]); but does not specifically teach wherein the indicator provides visual indication of the sample being within a specific, pre-defined pH range. However, pH indicators to provide a visual indication that a sample is within a specific, pre-defined pH range are well known in the art. It would have been obvious to a person of ordinary skill in the art during routine experimentation to test the pH during processing of a biological sample using a pH indicator.

Regarding claim 4, Taylor teaches the method of claim 1, wherein said indicator is a dye (para [0050]).

Regarding claim 5, Taylor teaches the method of claim 4, wherein said dye is a triarylmethane dye (para [0214]).

Regarding claim 6, Taylor teaches the method of claim 4, wherein said dye is selected from the group consisting of methyl violet 2B, methyl violet 6B, methyl violet 10B, pararosaniline, fuchsine, new fuchsine, fuchsine acid, phenol red, chlorophenol red, cresol red, malachite green (para [0215]), and brilliant green.

Regarding claim 8, Taylor teaches the method of claim 1, further comprising freezing said sample prior to said assessing step (para [0048]).

Regarding claim 11, Taylor teaches the method of claim 1, wherein said assessing step is performed by observing a color change in the sample (para [0123]).

Regarding claim 12, Taylor teaches the method of claim 11, wherein color change is monitored by eye (para [0123]).

Regarding claim 13, Taylor teaches the method of claim 11, wherein color change is monitored by automatic means (para [0123]).

Claims 2, 3, 7, and 9-10 lack an inventive step under PCT Article 33(3) as being obvious over Taylor in view of US 2008/0176209 A1 to Muller et al. (hereinafter "Muller").

Regarding claim 2, Taylor teaches the method of claim 1, but does not teach further comprising assessing said indicator in order to determine whether the sample is frozen and if the pH range is appropriate; and delivering the sample to a laboratory if said indicator indicates that the sample is frozen. Muller teaches a method for processing a biological sample (para [0002], [0109]), such as cells, blood, nucleic acids, and stem cells (para [0003], [0109]), comprising the use of various detectable indicators (para [0020]) including dyes, such as phenol red (para [0020]), and color-based pH indicators (para [0142]) and delivering frozen samples from production to the site of use. (para [0006]). It would have been obvious to a person of ordinary skill in the art to combine references of similar inventions during routine experimentation and to recognize the use of freeze indicators in the delivery of samples to a laboratory.

Regarding claim 3, Taylor teaches the method of claim 1, but does not teach further comprising the step of assessing said indicator in order to determine a position of said cells in a vial containing the sample. Muller teaches a method for processing a biological sample (para [0002], [0109]), such as cells, blood, nucleic acids, and stem cells (para [0003], [0109]), comprising the use of various detectable indicators (para [0020]) including dyes, such as phenol red (para [0020]), color-based pH indicators (para [0142]), and fluorescent and luminescent indicators (para [0020]) and delivering frozen samples from production to the site of use (para [0006]). It would have been obvious to a person of ordinary skill in the art to combine references of similar inventions during routine experimentation and to recognize the use of detectable indicators such as fluorescent or luminescent indicators to determine position of cells in a sample.

----------Continued below in Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 15/50964

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2) Citations and Explanations

Regarding claim 7, Taylor teaches the method of claim 1, but does not teach further comprising the steps of lysing the cell in order to liberate nucleic acid; and performing an analysis on the nucleic acid. Muller teaches a method for processing a biological sample (para [0002], [0109]), such as cells, blood, nucleic acids, and stem cells (para [0003], [0109]), comprising the use of various detectable indicators (para [0020]) including dyes, such as phenol red (para [0020]), color-based pH indicators (para [0142]), and fluorescent and luminescent indicators (para [0020]) and delivering frozen samples from production to the site of use (para [0006]). Muller further teaches a cell lysis buffer comprising a detergent, such as sodium dodecyl sulfate (para [0207], [0210]), and performing analysis on biological samples, including nucleic acids (para [0002], [0109]). It would have been obvious to a person of ordinary skill in the art to combine references for similar inventions during routine experimentation and recognize the well known practice of lysing a cell to liberate nucleic acid and performing analysis on the nucleic acid.

Regarding claim 9, Taylor teaches the method of claim 1, but does not teach further comprising the steps of: adding an alkaline lysis solution that optionally contains said indicator; optionally assessing pH of sample; neutralizing the lysis solution with a solution that optionally contains said indicator; and optionally assessing pH of the sample. Muller teaches a method for processing a biological sample (para [0002], [0109]), such as cells, blood, nucleic acids, and stem cells (para [0003], [0109]), comprising the use of various detectable indicators (para [0020]) including dyes, such as phenol red (para [0020]), color-based pH indicators (para [0142]), and fluorescent and luminescent indicators (para [0020]) and delivering frozen samples from production to the site of use (para [0006]). Muller further teaches a cell lysis buffer comprising a detergent, such as sodium dodecyl sulfate (para [0207], [0210]). Additionally, using an alkaline solution to lyse cells in a sample and thereafter neutralizing the pH of the sample for storage or further processing is well known in the art (see US 8,778,609 B1 (UMBARGER) col 4, ln 3-7; col 5, ln 2-5). It would have been obvious to a person of ordinary skill in the art to combine references during routine experimentation and recognize an alkaline lysis solution to lyse cells and thereafter neutralizing the sample.

Regarding claim 10, Taylor teaches the method of claim 1, but does not teach further wherein said cell is an embryonic cell. Muller teaches a method for processing a biological sample (para [0002], [0109]), such as cells, blood, nucleic acids, and stem cells (para [0003], [0109]), comprising the use of various detectable indicators (para [0020]) including dyes, such as phenol red (para [0020]), color-based pH indicators (para [0142]), and fluorescent and luminescent indicators (para [0020]) and delivering frozen samples from production to the site of use (para [0006]).). It would have been obvious to a person of ordinary skill in the art to combine references during routine experimentation to improve performance and utility of the invention.

Claim 14 lacks an inventive step under PCT Article 33(3) as being obvious over Taylor in view of US 2009/0301382 A1 (Patel).

Regarding claim 14, Taylor teaches the method of claim 1, but does not teach wherein said assessing step is performed by monitoring electrical conductivity in the sample. Patel teaches a system to indicate status of biological samples, such as freezing (para [0478]), wherein the indicator is a dye (para [0052]) and color change includes changes in conductivity (para [0053]). It would have been obvious to a person of ordinary skill in the art to combine references for similar inventions during routine experimentation to improve performance and utility of the invention.

Claims 1-14 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	07 JAN 2015
Applicant's or agent's file reference GSGE-019/01WO 29258/106	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 14/60256	International filing date *(day/month/year)* 13 October 2014 (13.10.2014)
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-019/01WO 29258/106	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 14/60256	International filing date *(day/month/year)* 13 October 2014 (13.10.2014)	(Earliest) Priority Date *(day/month/year)* 18 October 2013 (18.10.2013)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/60256

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; C12P 19/34; C07H 21/02; C40B 30/04 (2014.01)
CPC - C12Q 1/6883, 1/686; C07H 21/00; B01J 2219/00585
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
CPC: C12Q 1/6883, 1/686; C07H 21/00; B01J 2219/00585

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC: C12Q 1/6883, 1/686; C07H 21/00; B01J 2219/00585 (text search)
USPC: 435/6.11, 91.2; 536/23.1; 506/9 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PatBase; Google Patents; Google Scholar
Search terms: molecular inversion probe, target, paralog, homolog, pseudogene, training set, single nucleotide polymorphism (SNP), sequencing by synthesis (SBS), single molecule sequencing, SNVer, SOAPsnp

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	NUTTLE et al. Rapid and accurate large-scale genotyping of duplicated genes and discovery of interlocus gene conversions. Nat Methods ePub 28 July 2013 Vol 10 No 9 Pages 903-909 [using NCBI author copy pg 1-25 and Supplemental Pages] Especially abstract, pg 2 para 3, pg 3 para 2, pg 9 para 3, pg 20 fig 1, PDF pg 45-46 fig Supple Fig 10.	1, 3-5, 11, 13 , 14 ---------- 2, 6-10, 12, 15-20
Y	CHALLIS et al. An integrative variant analysis suite for whole exome next-generation sequencing data. BMC Bioinformatics 12 January 2012 Vol 13 No 8 Pages 1-12. Especially pg 10 col 1 para 2.	2, 12
Y	LIU et al. Comparison of next-generation sequencing systems. ePub 5 July 2012 Vol 2012 No 251364 Pages Especially see pg 3 Table 1(a): pg 5 col 2 para 3, pg 7 col 1 para 3	6, 15
Y	US 2012/0214678 A1 (RAVA et al.) 23 August 2012 (23.08.2012). Especially para [0016].	7-10, 16-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2014 (18.12.2014)	07 JAN 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 JAN 2015
Applicant's or agent's file reference GSGE-019/01WO 29258/106	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 14/60256	13 October 2014 (13.10.2014)	18 October 2013 (18.10.2013)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68; C12P 19/34; C07H 21/02; C40B 30/04 (2014.01)
CPC - C12Q 1/6883, 1/686; C07H 21/00; B01J 2219/00585

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	18 December 2014 (18.12.2014)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 14/60256

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 14/60256

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 6-10, 12, 15-20	YES
	Claims	1, 3-5, 11, 13, 14	NO
Inventive step (IS)	Claims	1-20	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 3-5, 11, 13 and 14 lack novelty under PCT Article 33(2) as being anticipated by the publication titled "Rapid and accurate large-scale genotyping of duplicated genes and discovery of interlocus gene conversions" by NUTTLE et al. (hereinafter "Nuttle").

As to claim 1, Nuttle teaches method for assessing a genomic region of a subject (abstract; "We developed a sequencing-based method for rapid and high-throughput genotyping of duplicated genes using molecular inversion probes designed to unique paralogous sequence variants. We apply this method to genotype all members of two gene families, SRGAP2 and RH, among a diversity panel of 1,056 humans. The approach can accurately distinguish copy number in paralogs having up to about 99.6% sequence identity, identify small gene-disruptive deletions, detect single nucleotide variants"), the method comprising:
obtaining a sample comprising nucleic acid from a subject, the nucleic acid comprising a target sequence from a target genomic region and a paralogous sequence from a non-target genomic region (pg 2 col 4-" We designed MIPs [i.e. Molecular Inversion Probes] to hybridize to sequence that is identical between paralogs (Fig. 1b), such that the probability of an individual MIP capturing sequence (Fig. 1c) from a particular paralog is a function of its copy number relative to the copy number of related paralogs. Massively parallel sequencing of amplified capture products allows simultaneous quantification of sequences derived from each paralog (Fig. 1d) and detection of sequence-level genetic variation. We selected two gene families to demonstrate proof-of-principle of our approach and to assess its power to discover novel genetic variation in duplicated regions: SRGAP2 a highly identical (> 99%) human specific gene family");
isolating the target sequence and the paralogous sequence from the sample (pg 20 fig 1 ii and iii; pg 2 col 4-" We designed MIPs to hybridize to sequence that is identical between paralogs (Fig. 1b), such that the probability of an individual MIP capturing sequence (Fig. 1c) from a particular paralog is a function of its copy number relative to the copy number of related paralogs);
sequencing the target sequence and the paralogous sequence to obtain sequence reads that comprise target sequence reads and paralogous sequence reads (pg 20 fig 1 iii and iv);
excluding the paralogous sequence reads (PDF pg 45-46 Suppl Fig 10b-"If the MLPA-MIP were designed such that the final base of one hybridization arm was complementary to a SUN, this assay might be able to achieve paralog-specificity [or specific target specificity]); and assessing the genomic region of the subject based on the target sequence reads (abstract; "The approach can accurately distinguish copy number in paralogs having up to about 99.6% sequence identity, identify small gene-disruptive deletions, detect single nucleotide variants").

As to claim 3, Nettle further teaches that isolating comprising conducting an assay that uses molecular inversion probes [i.e. MIPs] (pg 2 para 3; " Our approach leverages SUN [i.e. singly unique nucleotide] variants, fixed paralogous sequence variants that uniquely tag a specific paralog, distinguishing it from all other copies1. We systematically design MIP assays targeting SUNs across the length of the duplicated segment (Fig. 1a and Methods) and additional MIP assays targeting exons. We designed MIPs to hybridize to sequence that is identical between paralogs (Fig. 1b), such that the probability of an individual MIP capturing sequence (Fig. 1c) from a particular paralog is a function of its copy number relative to the copy number of related paralogs"; pg 20 fig 1 illustration).

As to claim 4, Nuttle further teaches the assay comprises: hybridizing molecular inversion probes to the target sequence and the paralogous sequence (pg 2 para 3; pg 20 fig 1 ii; PDF pg 45-46 Suppl Fig 10)
circularizing the hybridized probes (pg 20 fig 1 iii; PDF 44-45 Suppl Fig 10)
isolating the circularized probes (pg 9 para 3; Incubation of capture reactions at 60C was performed for 23-24 h, and incubation of exonuclease reactions at 37C was performed for 45 min [i.e. to remove linear [non-reacted probes]); and
linearizing the circularized probes (pg PDF pg 45 Suppl Fig 10).

As to claim 5, Nuttle further teaches the instrumentation utilized for sequencing is the Illumina HySeq 2000 or MiSeq (pg 3 para 2; "All captured sequences from a given DNA sample were barcoded, pooled with those from other samples, and sequenced using Illumina HiSeq or MiSeq to an approximate coverage of 350 reads per MIP per individual"), both known in the art to employ sequencing by synthesis [see "A" document titled "Comparison of next-generation sequencing systems" by LIU et al. (hereinafter "Liu"); see pg 3 Table 1(a): HySeq 2000 is indicted to use the "sequencing by synthesis" [i.e. SBS] method; pg 5 col 2 para 3: MiSeq is also indicated to use SBS).

----------continued in Supplemental Box------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 14/60256

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
Claim 6 is interpreted to depend from claim 5, not claim 4 as is written in the application, because claim 6 requres antecedent precedent to "sequencing by synthesis". Claim 5, but not claim 4,provides the requisite antecedent precedence.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 14/60256

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V-2 (Citations and Explanations)

As to claim 11, Nuttle teaches a method for assessing a genomic region of a subject (abstract), the method comprising: obtaining sequence reads that comprise target sequence reads and paralogous sequence reads (pg 2 para 4 and pg 20 fig 1 iii-iv); excluding the paralogous sequence reads (PDF pg 45-46 fig 10b; -"If the MLPA-MIP were designed such that the final base of one hybridization arm was complementary to a SUN, this assay might be able to achieve paralog-specificity [or specific target specificity]) and assessing a genomic region of a subject based on the target sequence reads (PDF pg 46 Suppl Fig 10 legend b; If the MLPA-MIP were designed such that the final base of one hybridization arm was complementary to a SUN, this assay might be able to achieve paralog-specificity [or specific target specificity]).

As to claim 13, Nuttle further teaches that the sequence reads are generated by sequencing nucleic acid from a sample from the subject using a sequencing instrument (pg 3 para 2; "All captured sequences from a given DNA sample were barcoded, pooled with those from other samples, and sequenced using Illumina HiSeq or MiSeq to an approximate coverage of 350 reads per MIP per individual").

As to claim 14, Nuttle further teaches the instrumentation utilized for sequencing is the Illumina HySeq 2000 or MiSeq (pg 3 para 2; "All captured sequences from a given DNA sample were barcoded, pooled with those from other samples, and sequenced using Illumina HiSeq or MiSeq to an approximate coverage of 350 reads per MIP per individual"), both known in the art to employ sequencing by synthesis. [see prior art reference "A" by Liu: pg 3 Table 1(a): HySeq 2000 is indicted to use the "sequencing by synthesis" [i.e. SBS] method; pg 5 col 2 para 3: MiSeq is also indicated to use SBS).

Claims 2 and 12 lack an inventive step under PCT Article 33(3) as being obvious over Nuttle, in view of the publication titled " An integrative variant analysis suite for whole exome next-generation sequencing data" by CHALLIS et al. (hereinafter "Challis").

As to claims 2 and 12, Nuttle teaches that excluding comprises selecting a MIP which will only hybridize to one of a set of paralogous genes (pg 45-46 Supple fig 10b; "If the MLPA [i.e. multiplex ligation-dependent probe amplification]-MIP were designed such that the final base of one hybridization arm was complementary to a SUN, this assay might be able to achieve paralog-specificity". Nuttle does not teach the specific claim limitations. However, Chaillis teaches creating a training set of target sequence reads (pg 10 col 1 para 2; "SNP training data: The SNP logistic regression models were trained using a set of 10 overlapping samples from the 1000 Genomes Exon Pilot project (Exon) and the 1000 Genomes Exome project (Exome) [...] The TP [i.e. total positive] was made up of all the SNP candidate sites in Exome data having at least two variant reads and confirmed by Exon SNP calls. The FP [i.e. false positive] comprised all other sites having at least two variant reads not confirmed by Exon SNP calls. In total, we have 6,516 TP and 347,154 FP in our training data set. Because the training data set is based on a continuous callable region, it represents the real TP/FP ratio in the sequencing data") identifying one or more common variants present in the training set of target sequence reads (pg 10 col 1 para 2 e.g. total positives or TPs), wherein common variants observed in the sequence reads that are not present in the training set of target sequence reads are of paralogous origin (pg 10 col 1 para 2; e.g. false positives or FP) calculating a frequency of sequence reads containing variants paralogous sequence reads (pg 10 col 1 para 2; i.e. TP/FP ratio) defining variant paralogous sequence reads to be excluded based on their frequency (pg 10 col 1 para 2); An artisan of ordinary skill in the art would have recognized that the training set method taught by Challis would have enabled excluding paralogous sequence reads based the defining step. Consequently, it would have been obvious for one of ordinary skill in the art to combine a method of excluding, as taught by Nuttle, with all of the claim elements, as taught by Challis, because it would have enabled variants of paralgous sequence reads to be excluded.

Claims 6 and 15 lack an inventive step under PCT Article 33(3) as being obvious over Nuttle, in view of the article titled "Comparison of next-generation sequencing systems" by LIU et al. (hereinafter "Liu").

As to claims 6 and 15, Nuttle teaches that the method of sequencing is sequencing by synthesis (pg 3 para 2; Illumina HySeq 2000 and MiSeq). Nuttle does not teach sequencing by synthesis is single molecule sequencing by synthesis. However, Liu teaches single molecule synthesis (pg 7 col 1 para 3; " Single-molecule real-time (SMRT) is the third-generation sequencing method developed by Pacific Bioscience"). An artisan of ordinary skill in the art would have recognized that single molecule sequencing was well known in the art, as exemplified in the review by Liu, such that it would have been obvious that single molecule synthesis by sequencing could have been incorporated into the protocol utilized by Nuttle without undue effort, to enable a single DNA molecule to be utilized as a template.

Claims 7-10 and 16-20 lack an inventive step under PCT Article 33(3) as being obvious over Nuttle, in view of US 2012/0214678 A1 to RAVA et al. (hereinafter "Rava").

As to claims 7 and 16, Nuttle teaches that the sample is a human DNA sample (abstract). Nuttle does not specifically teach that the sample is a human body fluid sample. However, Rava teaches that the sample is a human body fluid sample (para [0016]; The maternal sample is selected from blood, plasma, serum, urine and saliva"). An artisan of ordinary skill would have recognized that the method of Nuttle could have utilized DNA sample from any sample, including human body fluid sample. Consequently, it would have been obvious for one of ordinary skill in the art to combine a human DNA sample, as taught by Nuttle, with the sample is a human body fluid sample, because it would have enabled a convenient and accessible source of DNA for diagnostic testing.

As to claim 8 and 18, Rava further teaches that the sample is a maternal blood sample (para [0016]).
----------continued in next Supplemental Box----------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 14/60256

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
previous Supplemental Box

As to claim 9 and 19, Rava further teaches that the maternal blood sample comprises cell free circulating nucleic acid (para [0016]; " In one embodiment, the invention provides a method for determining the fraction of fetal nucleic acids in a maternal sample comprising a mixture of fetal and maternal genomic DNA e.g. cell-free DNA").

As to claim 10 and 20, Rava further teaches that at least a portion of the cell free circulating nucleic acid is from a fetus being carried the subject (para [0016]).

As to claim 17, Rava further teaches that the body fluid sample comprises cell free circulating nucleic acid (para [0016]).

Claims 1-20 have industrial applicability as defined in PCT Article 33(4) because the subject matter can be made or used by industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-028/01WO 29258/156	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2016/012286**	International filing date *(day/month/year)* **06 January 2015 (06.01.2015)**	(Earliest) Priority Date *(day/month/year)* 06 January 2015 (06.01.2015)
Applicant **GOOD START GENETICS, INC.**		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **3** sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/012286

A. CLASSIFICATION OF SUBJECT MATTER

C12Q 1/68(2006.01)i, C12N 9/00(2006.01)i, C12N 9/22(2006.01)i, G06F 19/18(2011.01)i, G06F 19/22(2011.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q 1/68; C12P 19/34; C12N 9/00; C12N 9/22; G06F 19/18; G06F 19/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: molecular inversion probes (MIPs), structural variant, screening, inter-probe

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 8778609 B1 (GOOD START GENETICS, INC.) 15 July 2014 See abstract; claims 1-15; column 8; and figures 1-2.	1-29
A	SHEN et al., 'Multiplex target capture with double-stranded DNA probes' Genome Medicine, Vol.5, No.50 (internal pages 1-8) (2013) See abstract; pages 2-4; and figure 1.	1-29
A	YOON et al., 'MicroDuMIP: target-enrichment technique for microarray-based duplex molecular inversion probes' Nucleic Acids Research, Vol.43, No.5, e28 (internal pages 1-9) (e-pub. 20 November 2014) See the whole document.	1-29
A	LIN et al., 'A molecular inversion probe assay for detecting alternative splicing' BioMed Central (BMC) Genomics, Vol.11, No.712 (internal pages 1-14) (2010) See the whole document.	1-29
A	UMBARGER et al., 'Next-generation carrier screening' Genetics in Medicine, Vol.16, No.2, pp.132-140 (2014) See the whole document.	1-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2016 (29.04.2016)	**04 May 2016 (04.05.2016)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
CHO, KI YUN
Telephone No. +82-42-481-5655

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/012286

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 8778609 B1	15/07/2014	US 2014-0308667 A1	16/10/2014
		US 2015-0354003 A1	10/12/2015
		US 9115387 B2	25/08/2015
		WO 2014-152421 A1	25/09/2014

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS G.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**04 May 2016 (04.05.2016)**
Applicant's or agent's file reference: GSGE-028/01WO 29258/156	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/012286	**06 January 2015 (06.01.2015)**	06 January 2015 (06.01.2015)

International Patent Classification (IPC) or both national classification and IPC

C12Q 1/68(2006.01)i, C12N 9/00(2006.01)i, C12N 9/22(2006.01)i, G06F 19/18(2011.01)i, G06F 19/22(2011.01)i

Applicant
GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea Facsimile No. +82-42-481-8578	29 April 2016 (29.04.2016)	CHO, KI YUN Telephone No. +82-42-481-5655

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/012286

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:
      ☐ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/012286

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-29	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-29	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-29	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: US 8778609 B1 (GOOD START GENETICS, INC.) 15 July 2014

D2: Genome Medicine, Vol.5, No.50 (internal pages 1-8) (2013)

D3: Nucleic Acids Research, Vol.43, No.5, e28 (internal pages 1-9) (e-pub. 20 November 2014)

D4: BioMed Central (BMC) Genomics, Vol.11, No.712 (internal pages 1-14) (2010)

D5: Genetics in Medicine, Vol.16, No.2, pp.132-140 (2014)

1. Novelty and Inventive Step

1.1. Claims 1-29

Claims 1, 16, 23 and 26 relate to a method of identifying a structural variant (claims 1 and 16) and splice form (claims 23 and 26), by using an inter-probe product which is created by connecting together two of molecular inversion probes (MIPs) via arms that have hybridized to the same molecule.

None of the prior art documents disclose or suggest the inter-probe product for identifying the structural variant and the splice form. Moreover, the applicant has shown that the feature in claims 1, 16, 23 and 26 produces an beneficial effect, detecting large chromosomal abnormalities without exonuclease digestion, compared to conventional MIPs in the art. Accordingly, the subject matter of claims 1, 16, 23 and 26 is neither anticipated nor rendered obvious by the prior art documents, taken alone or in combination.

Therefore, claims 1, 16, 23 and 26 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

Continued on Supplemental Box

Petitioner Illumina, Inc., EX1003, p. 713

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Box No. V

Claims 2-15, 17-22, 24-25 and 27-29, respectively dependent on claims 1, 16, 23 and 26, also meet the requirements of PCT Article 33(2) and 33(3).

2. Industrial Applicability

Claims 1-29 are industrially applicable under PCT Article 33(4).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-024/01WO 29258/136	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2015/045247**	International filing date *(day/month/year)* **14 August 2015 (14.08.2015)**	(Earliest) Priority Date *(day/month/year)* 15 August 2014 (15.08.2014)
Applicant **GOOD START GENETICS, INC.**		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **3** sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. **3**
      ☐ as suggested by the applicant.
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/045247

A. CLASSIFICATION OF SUBJECT MATTER

G06F 19/28(2011.01)i, G06F 19/26(2011.01)i, G06F 19/18(2011.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G06F 19/28; G06F 19/00; G06F 19/18; G06F 19/24; H04L 12/56; G06F 19/26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: genome, mutation, graph, pointer, database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004-015609 A2 (DAVID ATLAN et al.) 19 February 2004 See page 12, lines 10-12; page 22, lines 20-21; page 25, lines 10-30; and figure 4.	1-25
Y	US 2012-0236861 A1 (LAWRENCE GANESHALINGAM et al.) 20 September 2012 See paragraphs [0055], [0127]; and figure 4.	1-25
Y	US 2013-0332081 A1 (MARTIN G. REESE et al.) 12 December 2013 See paragraphs [0038]-[0040]; and figures 1-7.	9,10,23
A	US 2014-0136120 A1 (COSMOSID INC.) 15 May 2014 See paragraphs [0071]-[0086]; and figures 1-4.	1-25
A	US 2014-0222349 A1 (ASSURERX HEALTH, INC.) 07 August 2014 See paragraphs [0055]-[0168]; and figures 1A-8.	1-25

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2015 (16.11.2015)	**16 November 2015 (16.11.2015)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
KIM, Seung Beom
Telephone No. +82-42-481-3371

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2015/045247

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004-015609 A2	19/02/2004	AU 2003-282562 A1	25/02/2004
		WO 2004-015609 A3	19/05/2005
US 2012-0236861 A1	20/09/2012	US 2012-230326 A1	13/09/2012
		US 2012-230338 A1	13/09/2012
		US 2012-230339 A1	13/09/2012
		US 2012-232874 A1	13/09/2012
		US 2012-233201 A1	13/09/2012
		US 2012-233202 A1	13/09/2012
		US 8982879 B2	17/03/2015
		WO 2012-122546 A2	13/09/2012
		WO 2012-122546 A3	03/01/2013
		WO 2012-122547 A2	13/09/2012
		WO 2012-122547 A3	15/11/2012
		WO 2012-122548 A2	13/09/2012
		WO 2012-122548 A3	15/11/2012
		WO 2012-122549 A2	13/09/2012
		WO 2012-122549 A3	15/11/2012
		WO 2012-122551 A2	13/09/2012
		WO 2012-122551 A3	06/12/2012
		WO 2012-122553 A2	13/09/2012
		WO 2012-122553 A3	29/11/2012
		WO 2012-122555 A2	13/09/2012
		WO 2012-122555 A3	27/12/2012
US 2013-0332081 A1	12/12/2013	EP 2614161 A1	17/07/2013
		EP 2614161 A4	26/08/2015
		WO 2012-034030 A1	15/03/2012
US 2014-0136120 A1	15/05/2014	EP 2668320 A1	04/12/2013
		US 2012-004111 A1	05/01/2012
		US 8478544 B2	02/07/2013
		WO 2012-103189 A1	02/08/2012
US 2014-0222349 A1	07/08/2014	WO 2014-113522 A1	24/07/2014

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**16 November 2015 (16.11.2015)**
Applicant's or agent's file reference: GSGE-024/01WO 29258/136	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2015/045247	**14 August 2015 (14.08.2015)**	15 August 2014 (15.08.2014)

International Patent Classification (IPC) or both national classification and IPC

G06F 19/28(2011.01)i, G06F 19/26(2011.01)i, G06F 19/18(2011.01)i

Applicant
GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea Facsimile No. +82-42-472-7140	16 November 2015 (16.11.2015)	KIM, Seung Beom Telephone No. +82-42-481-3371

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/045247

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:
      ☐ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2015/045247

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-25	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-25	NO
Industrial applicability (IA)	Claims	1-25	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: WO 2004-015609 A2 (DAVID ATLAN et al.) 19 February 2004
D2: US 2012-0236861 A1 (LAWRENCE GANESHALINGAM et al.) 20 September 2012
D3: US 2013-0332081 A1 (MARTIN G. REESE et al.) 12 December 2013
D4: US 2014-0136120 A1 (COSMOSID INC.) 15 May 2014
D5: US 2014-0222349 A1 (ASSURERX HEALTH, INC.) 07 August 2014

1. Novelty and Inventive Step

1.1. Claim 1

D1, which is considered to be the closest prior art to the subject matter of claim 1, discloses that a system for describing genetic information comprises:
at least one computer comprising memory coupled to a processor, the system having at least a portion of a graph database stored therein, wherein the system is operable to:
obtain data representing a mutation in a genome of an individual ("finding mutations"; see page 25, line 30 in D1); and
use a node in the graph database to store a description of the mutation ("graphical data showing the mutation found sequencing technology used to detect mutation"; see page 25, lines 10-12 in D1).

The other features of claim 1 are not explicitly disclosed in D1, but the features can be easily derived from the features of D1 and D2 in analogous art as follows:
storing, in the node, a pointer to an adjacent node that provides information about a clinical

Continued on Supplemental Box

Petitioner Illumina, Inc., EX1003, p. 720

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Box No. V

significance of the mutation ("using a pointer table"; see paragraph [0127] and figure 4 in D2); and

querying the graph database to provide a report of the clinical significance of the mutation in the genome of the individual ("looking up in a list or in a database whether the mutation is known"; see page 22, lines 20-21 in D1).

Accordingly, it would be obvious to a person skilled in the art to combine the disclosures of D1 and D2, thereby arriving at the claim. Therefore, claim 1 lacks an inventive step under PCT Article 33(3).

1.2. Claims 2-15

Claims 2-15 are directly or indirectly dependent on claim 1.

The additional feature of claim 2 can be easily derived from the feature of D1 ("determining mutation for bases at determined positions of the base sequence of the patient list"; see page 12, lines 10-12).

The additional feature of claim 3 can be easily derived from the feature of D2 ("using a pointer table and graph"; see paragraph [0127] and figure 4).

The additional feature of claim 4 can be easily derived from the feature of D1 ("looking up in a list or in a database whether the mutation is known"; see page 22, lines 20-21).

The additional feature of claim 5 can be easily derived from the feature of D2 ("the DNA sequence entries may be stored as BAM, SRF, fastq as well as in the FASTA format"; see paragraph [0055]).

The additional features of claims 6 and 7 can be easily derived from the feature of D2 ("using a pointer table and graph"; see paragraph [0127] and figure 4).

The additional feature of claim 8 can be easily derived from the feature of D1 ("looking up in a list or in a database whether the mutation is known"; see page 22, lines 20-21).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Previous Page

The additional feature of claim 9 is not explicitly disclosed in D1 or D2, but this feature can be easily derived from the feature of D3 in analogous art ("a variant call format (VCF) file"; see paragraph [0038]).

The additional feature of claim 10 can be easily derived from the feature of D2 ("using a pointer table and graph"; see paragraph [0127] and figure 4).

The additional features of claims 11 and 12 are merely a matter of design option in view of the feature of D1 ("graphical data showing the mutation found sequencing technology used to detect mutation"; see page 25, lines 10-12).

The additional feature of claim 13 can be easily derived from the feature of D2 ("using a pointer table and graph"; see paragraph [0127] and figure 4).

The additional feature of claim 14 is merely a matter of design option in view of the feature of D1 ("graphical data showing the mutation found sequencing technology used to detect mutation"; see page 25, lines 10-12).

The additional feature of claim 15 can be easily derived from the feature of D2 ("using a pointer table and graph"; see paragraph [0127] and figure 4).

Accordingly, it would be obvious to a person skilled in the art to combine the disclosures of D1 and D2 to arrive at claims 2-8, 11-15, and it would be obvious to a person skilled in the art to combine the disclosures of D1, D2 and D3 to arrive at claims 9 and 10. Therefore, claims 2-15 lack an inventive step under PCT Article 33(3).

1.3. Claim 16

The features of claim 16 are substantially the same as those of claim 1 except for the categories of invention. Accordingly, it would be obvious to a person skilled in the art to combine the disclosures of D1 and D2, thereby arriving at the claim. Therefore, claim 16 lacks an inventive step under PCT Article 33(3).

Continued on The Next Page

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Previous Page

1.4. Claims 17-25

Claims 17-25 are directly or indirectly dependent on claim 16.

The additional feature of claim 17 can be easily derived from the feature of D1 ("determining mutation for bases at determined positions of the base sequence of the patient list"; see page 12, lines 10-12).

The additional feature of claim 18 can be easily derived from the feature of D2 ("using a pointer table and graph"; see paragraph [0127] and figure 4).

The additional feature of claim 19 can be easily derived from the feature of D1 ("looking up in a list or in a database whether the mutation is known"; see page 22, lines 20-21).

The additional feature of claim 20 can be easily derived from the feature of D2 ("the DNA sequence entries may be stored as BAM, SRF, fastq as well as in the FASTA format"; see paragraph [0055]).

The additional feature of claim 21 can be easily derived from the feature of D2 ("using a pointer table and graph"; see paragraph [0127] and figure 4).

The additional feature of claim 22 can be easily derived from the feature of D1 ("looking up in a list or in a database whether the mutation is known"; see page 22, lines 20-21).

The additional feature of claim 23 is not explicitly disclosed in D1 or D2, but this feature can be easily derived from the feature of D3 in analogous art ("a variant call format (VCF) file"; see paragraph [0038]).

The additional features of claims 24 and 25 are merely a matter of design option in view of the feature of D1 ("graphical data showing the mutation found sequencing technology used to detect mutation"; see page 25, lines 10-12).

Accordingly, it would be obvious to a person skilled in the art to combine the disclosures of D1 and D2 to arrive at claims 17-22, 24, 25, and it would be obvious to a person skilled in

Continued on The Next Page

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Previous Page

the art to combine the disclosures of D1, D2 and D3 to arrive at claim 23. Therefore, claims 17-25 lack an inventive step under PCT Article 33(3).

2. Industrial Applicability

Claims 1-25 are industrially applicable under PCT Article 33(4).

ENTERED IN CPI

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 29 JAN 2015
Applicant's or agent's file reference GSGE-018/01WO 29258/100	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2014/060056	International filing date *(day/month/year)* 10 October 2014
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

29 JAN 2015

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-018/01WO 29258/100	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2014/060056	International filing date *(day/month/year)* 10 October 2014	(Earliest) Priority Date *(day/month/year)* 18 October 2013
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☐ as suggested by the applicant.
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/060056

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q-1/68 (2014.01)
CPC - C12Q-1/6883 (2014.11)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C12Q-1/68; C40B-30/00, 30/04, 40/06 (2014.01)
USPC - 435/6.1, 6.11, 287.2; 506/2, 16; 702/19, 181

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C12Q-1/68, 1/6813, 1/6874, 1/6876, 1/6883; C12Q-2600/156 (2014.11) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Patents, Google Scholar, Google.
Search terms used: copy number, molecular inversion probe, capture, DNA, normalize, diploid, carrier status, disease, stable, altered

C. DOCUMENTS CONSIDERED TO BE RELEVANT

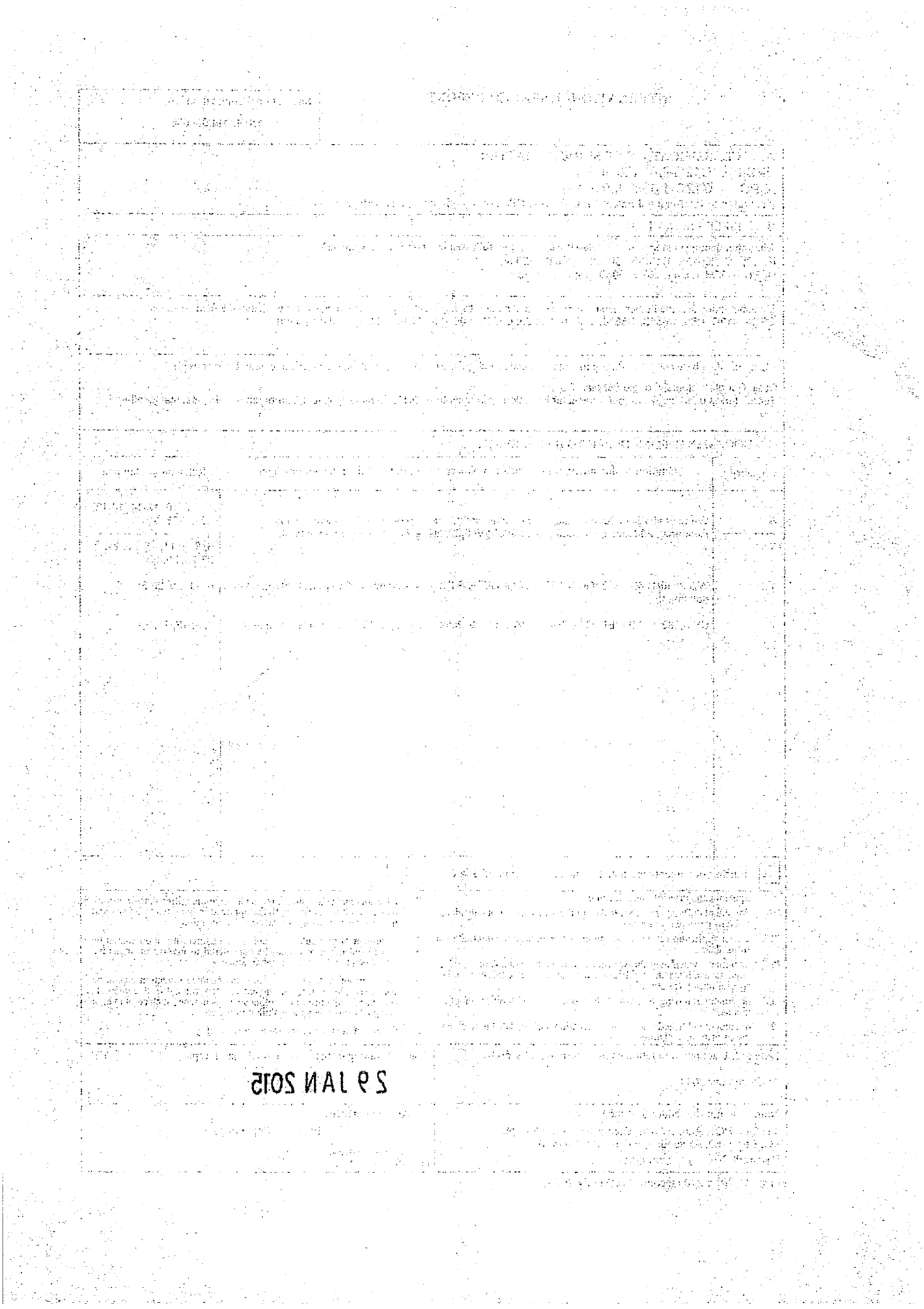
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Wang et al. Allele quantification using molecular inversion probes (MIP). Nucleic Acids Research, 28 November 2005 (28.11.2005) Vol. 33, Issue 21, e183, entire document.	1-5, 7, 10, 12-14, 16-19, 22, 26-28, 31
Y		6, 8, 9, 11, 15, 20, 21, 23-25, 29, 30
Y	WO 2010/126614 A2 (GOOD START GENETICS INC) 04 November 2010 (04.11.2010), entire document	6, 11, 20, 23-25, 29
Y	US 8,283,116 B1 (BHATTACHARYYA et al) 09 October 2012 (09.10.2012), entire document	8, 9, 15, 21, 30

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2014	29 JAN 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)


29 JAN 2015

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	29 JAN 2015
Applicant's or agent's file reference GSGE-018/01WO 29258/100	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2014/060056	10 October 2014	18 October 2013

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2014.01)
CPC - C12Q 1/6883 (2014.12)

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to th IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	15 December 2014	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

29 JAN 2015

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/060056

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/060056

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	6, 8, 9, 11, 15, 20, 21, 23-25, 29, 30	YES
	Claims	1-5, 7, 10, 12-14, 16-19, 22, 26-28, 31	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-31	NO
Industrial applicability (IA)	Claims	1-31	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-5, 7, 10, 12-14, 16-19, 22, 26-28, and 31 lack novelty under PCT Article 33(2) as being anticipated by Wang et al. (hereafter Wang).

Regarding claim 1, Wang discloses a method for determining copy number state of one or more genes in a sample (detection of genomic copy number changes has been an important research area, Pg. 1), the method comprising the steps of: exposing a sample to a plurality of molecular inversion probes (we apply the molecular inversion probes (MIP) technology to copy number analysis, Pg. 1) capable of capturing DNA from at least one genomic region suspected of having an altered copy number and at least one internal control DNA known or suspected to have a stable copy number (MIP probes have two specific homology sequences that leave a 1 bp gap when hybridized to the genome. They also contain specific tag sequences that are ultimately read on the microarray, Pg. 1); capturing DNA that binds said molecular inversion probes (the probes are hybridized, Pg. 1); sequencing DNA obtained in said capture step (after eliminating the linear probes with exonucleases, PCRs using the common primers that now face each other is performed in the four tubes. In addition to signal amplification a fluorescent label is introduced by a PCR primer in each of the four tubes. The four reactions are then mixed and hybridized onto a tag array. As many as 22,000 single nucleotide polymorphism (SNP) markers from an individual sample can be interrogated, Pg. 1); normalizing read counts obtained in said sequencing step for said at least one genomic region with respect to said internal control DNA (using the reference samples the average signal in each of the three clusters (two homozygous clusters and a heterozygous cluster) for each marker as well as the standard deviation of the signal after removing (15%) outliers are calculated, Pg. 2); comparing said normalized read counts to read counts for at least one control diploid locus (the average signal in a cluster is then set to denote two copies since most reference samples will be diploid at any given point in the genome, Pg. 2); and determining a copy number state of said at least one genomic region (copy sum analysis is a way of measuring total copy number irrespective of allele ratio . . . for each allele, we perform a straight line fit (using linear regression) of the reference sample signals against their genotype cluster membership . . . This provides us with a background signal (Y-intercept) and signal per copy (slope) for each allele so that any signal level for any given allele of any marker in any sample can be mapped to a copy number of that allele. Summing the inferred copy numbers over both alleles give us, Pg. 2).

Regarding claim 2, Wang discloses the method of claim 1, wherein said determining step comprises determining differences between said normalized read counts for said at least one genomic region and said read counts for said at least one control diploid locus (the average signal in a cluster is then set to denote two copies since most reference samples will be diploid at any given point in the genome, Pg. 2) based upon said comparison (copy sum analysis is a way of measuring total copy number irrespective of allele ratio . . . for each allele, we perform a straight line fit (using linear regression) of the reference sample signals against their genotype cluster membership . . . This provides us with a background signal (Y-intercept) and signal per copy (slope) for each allele so that any signal level for any given allele of any marker in any sample can be mapped to a copy number of that allele. Summing the inferred copy numbers over both alleles give us, Pg. 2).

Regarding claim 3, Wang discloses the method of claim 1, wherein said normalized read counts for said at least one control diploid locus (the average signal in a cluster is then set to denote two copies since most reference samples will be diploid at any given point in the genome, Pg. 2) are obtained from said sample (copy sum analysis is a way of measuring total copy number irrespective of allele ratio . . . for each allele, we perform a straight line fit (using linear regression) of the reference sample signals against their genotype cluster membership . . . This provides us with a background signal (Y-intercept) and signal per copy (slope) for each allele so that any signal level for any given allele of any marker in any sample can be mapped to a copy number of that allele. Summing the inferred copy numbers over both alleles give us, Pg. 2).

Regarding claim 4, Wang discloses the method of claim 1, wherein said normalized read counts for said at least one control diploid locus are obtained from a separate sample that is different from said sample (In addition to the basic analysis for copy number and allele ratio at every SNP, we utilized data from the surrounding SNPs for 'smoothing', Pg. 4).

Regarding claim 5, Wang discloses the method of claim 4, wherein said normalized read counts for said at least one control diploid locus are obtained in silico (Processes of in silico and in vitro screening are required to obtain acceptable loci in these cases, limiting the reach and flexibility of these techniques. However, MIP has been developed as an efficient method for custom SNP genotyping, and is therefore suitable to assess copy number at high density in regions of interest, Pg. 13)).

Petitioner Illumina, Inc., EX1003, p. 733

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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Regarding claim 7, Wang discloses the method of claim 1, wherein said at least one genomic region comprises a first gene and a second gene, wherein said first and second genes are homologs, orthologs, or paralogs (features that are important for the utility of technologies assessing copy number changes include the ability to interrogate regions of interest at the desired density as well as the ability to differentiate the two homologs, Pg. 1).

Regarding claim 10, Wang discloses the method of claim 1, wherein said read counts for said at least one control diploid locus are determined empirically (copy sum analysis is a way of measuring total copy number irrespective of allele ratio . . . for each allele, we perform a straight line fit (using linear regression) of the reference sample signals against their genotype cluster membership . . . This provides us with a background signal (Y-intercept) and signal per copy (slope) for each allele so that any signal level for any given allele of any marker in any sample can be mapped to a copy number of that allele. Summing the inferred copy numbers over both alleles give us, Pg. 2).

Regarding claim 12, Wang discloses the method of claim 1, wherein said determining step comprises determining a difference between said copy number state of said at least one genomic region to a copy number distribution encompassing a plurality of stable control loci (In addition to the basic analysis for copy number and allele ratio at every SNP, we utilized data from the surrounding SNPs for 'smoothing', Pg. 4).

Regarding claim 13, Wang discloses the method of claim 1, wherein said sample is selected from blood and tissue (DNA purified from a standard blood control sample and three FFPE samples for normal brain, colon and liver, Pg. 13; FIG. 9).

Regarding claim 14, Wang discloses a method of determining copy number between two paralogous genes (the collection of allele information identifies alleles that are preferentially deleted or duplicated in a set of different samples. Such identification can allow the definition of the critical gene in a large genomic deletion or duplication, Pg. 13; Markers on chromosome 12 have on average a higher copy number and a lower allele ration than the surrounding chromosomes. This is consistent with a 'mosaic' duplication of chromosome 12 in a fraction of the cells, Pg. 8; FIG. 5), the method comprising the steps of: exposing a sample comprising a first genetic locus, a second genetic locus, and at least one control genetic locus to a plurality of molecular inversion probes (we apply the molecular inversion probes (MIP) technology to copy number analysis, Pg. 1), at least some of which are capable of hybridizing with one or more of said first genetic locus, said second genetic locus, and said control genetic locus (the probes are hybridized, Pg. 1; In addition to the basic analysis for copy number and allele ratio at every SNP, we utilized data from the surrounding SNPs for 'smoothing', Pg. 4); obtaining DNA that is hybridized to a member of said plurality of molecular inversion probes (MIP probes have two specific homology sequences that leave a 1 bp gap when hybridized to the genome. They also contain specific tag sequences that are ultimately read on the microarray, Pg. 1); sequencing said DNA (after eliminating the linear probes with exonucleases, PCRs using the common primers that now face each other is performed in the four tubes. In addition to signal amplification a fluorescent label is introduced by a PCR primer in each of the four tubes. The four reactions are then mixed and hybridized onto a tag array. As many as 22,000 single nucleotide polymorphism (SNP) markers from an individual sample can be interrogated, Pg. 1); normalizing read counts from said sequencing step for each of said first genetic locus and said second genetic locus with respect to said at least one control genetic locus (using the reference samples the average signal in each of the three clusters (two homozygous clusters and a heterozygous cluster) for each marker as well as the standard deviation of the signal after removing (15%) outliers are calculated, Pg. 2); comparing normalized read counts for each of said first genetic locus and said second genetic locus to normalized read counts for one or more control samples with a known number of copies of said first genetic locus and said second genetic locus (the average signal in a cluster is then set to denote two copies since most reference samples will be diploid at any given point in the genome, Pg. 2); and determining relative copy number of said first genetic locus and said second genetic locus based upon said comparing step (copy sum analysis is a way of measuring total copy number irrespective of allele ratio . . . for each allele, we perform a straight line fit (using linear regression) of the reference sample signals against their genotype cluster membership . . . This provides us with a background signal (Y-intercept) and signal per copy (slope) for each allel so that any signal level for any given allele of any marker in any sample can be mapped to a copy number of that allele. Summing the inferred copy numbers over both alleles give us, Pg. 2).

Regarding claim 16, Wang discloses the method of claim 14, wherein said at least one control genetic locus is one that has a stable copy number (In addition to the basic analysis for copy number and allele ratio at every SNP, we utilized data from the surrounding SNPs for 'smoothing', Pg. 4).

Regarding claim 17, Wang discloses the method of claim 14, further comprising the step of genotyping DNA from said sample (we first ran our genotype-calling algorithm on all the reference samples to generate genotype calls for each sample, Pg. 4).

Regarding claim 18, Wang discloses the method of claim 17, wherein said genotyping step is conducted in the same assay as said copy number determination (after eliminating the linear probes with exonucleases, PCRs using the common primers that now face each other is performed in the four tubes. In addition to signal amplification a fluorescent label is introduced by a PCR primer in each of the four tubes. The four reactions are then mixed and hybridized onto a tag array. As many as 22,000 single nucleotide polymorphism (SNP) markers from an individual sample can be interrogated, Pg. 1).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
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Regarding claim 19, Wang discloses the method of claim 17, wherein said genotyping step comprises assessing a genotype at one or more loci known or suspected to be associated with a disease for which copy number variation is diagnostic (detection of genomic copy number changes has been an important research area, Pg. 1; DNA copy number changes occur in human disease and particularly in cancer, Pg. 1).

Regarding claim 22, Wang discloses the method of claim 17, further comprising reporting carrier status for one or more conditions (detection of genomic copy number changes has been an important research area, Pg. 1; DNA copy number changes occur in human disease and particularly in cancer, Pg. 1).

Regarding claim 26, Wang discloses a method for determination of carrier status with respect to one or more conditions (detection of genomic copy number changes has been an important research area, Pg. 1; DNA copy number changes occur in human disease and particularly in cancer, Pg. 1), the method comprising the steps of: exposing a sample to a plurality of molecular inversion probes (we apply the molecular inversion probes (MIP) technology to copy number analysis, Pg. 1), at least some of which are capable of hybridizing to DNA of a first locus or DNA of a second locus (the probes are hybridized, Pg. 1); obtaining DNA in said sample that is hybridized to a member of said plurality of probes (MIP probes have two specific homology sequences that leave a 1 bp gap when hybridized to the genome. They also contain specific tag sequences that are ultimately read on the microarray, Pg. 1); sequencing said DNA, thereby to obtain sequence read counts for said first locus and said second locus (after eliminating the linear probes with exonucleases, PCRs using the common primers that now face each other is performed in the four tubes. In addition to signal amplification a fluorescent label is introduced by a PCR primer in each of the four tubes. The four reactions are then mixed and hybridized onto a tag array. As many as 22,000 single nucleotide polymorphism (SNP) markers from an individual sample can be interrogated, Pg. 1); normalizing said read counts with respect to a control locus, the copy number of which is stable (using the reference samples the average signal in each of the three clusters (two homozygous clusters and a heterozygous cluster) for each marker as well as the standard deviation of the signal after removing (15%) outliers are calculated, Pg. 2); comparing normalized read counts for said first locus and said second locus with a standard (the average signal in a cluster is then set to denote two copies since most reference samples will be diptoid at any given point in the genome, Pg. 2); and inferring copy number status of said first locus and said second locus based upon said comparing step (copy sum analysis is a way of measuring total copy number irrespective of allele ratio . . . for each allele, we perform a straight line fit (using linear regression) of the reference sample signals against their genotype cluster membership . . . This provides us with a background signal (Y-intercept) and signal per copy (slope) for each allel so that any signal level for any given allele of any marker in any sample can be mapped to a copy number of that allele. Summing the inferred copy numbers over both alleles give us, Pg. 2).

Regarding claim 27, Wang discloses the method of claim 26, further comprising obtaining a genotype of a third locus (In addition to the basic analysis for copy number and allele ratio at every SNP, we utilized data from the surrounding SNPs for 'smoothing', Pg. 4).

Regarding claim 28, Wang discloses the method of claim 26, further comprising obtaining a genotype of one or both of said first locus and said second locus (In addition to the basic analysis for copy number and allele ratio at every SNP, we utilized data from the surrounding SNPs for 'smoothing', Pg. 4).

Regarding claim 31, Wang discloses a method for determination of carrier status with respect to a condition (detection of genomic copy number changes has been an important research area, Pg. 1; DNA copy number changes occur in human disease and particularly in cancer, Pg. 1), the method comprising the steps of: exposing a sample to a plurality of molecular inversion probes (we apply the molecular inversion probes (MIP) technology to copy number analysis, Pg. 1), at least some of which are capable of hybridizing to DNA at each of a plurality of loci (the probes are hybridized, Pg. 1; In addition to the basic analysis for copy number and allele ratio at every SNP, we utilized data from the surrounding SNPs for 'smoothing', Pg. 4); obtaining DNA in said sample that is hybridized to a member of said plurality of probes (MIP probes have two specific homology sequences that leave a 1 bp gap when hybridized to the genome. They also contain specific tag sequences that are ultimately read on the microarray, Pg. 1); sequencing said DNA, thereby to obtain sequence read counts for at least some members of said plurality of loci (after eliminating the linear probes with exonucleases, PCRs using the common primers that now face each other is performed in the four tubes. In addition to signal amplification a fluorescent label is introduced by a PCR primer in each of the four tubes. The four reactions are then mixed and hybridized onto a tag array. As many as 22,000 single nucleotide polymorphism (SNP) markers from an individual sample can be interrogated, Pg. 1); normalizing said read counts with respect to a control locus, the copy number of which is stable (using the reference samples the average signal in each of the three clusters (two homozygous clusters and a heterozygous cluster) for each marker as well as the standard deviation of the signal after removing (15%) outliers are calculated, Pg. 2); comparing normalized read counts for members of said plurality with a standard (the average signal in a cluster is then set to denote two copies since most reference samples will be diploid at any given point in the genome, Pg. 2); and inferring copy number status of at least one member of said plurality based upon said comparing step (copy sum analysis is a way of measuring total copy number irrespective of allele ratio . . . for each allele, we perform a straight line fit (using linear regression) of the reference sample signals against their genotype cluster membership . . . This provides us with a background signal (Y-intercept) and signal per copy (slope) for each allel so that any signal level for any given allele of any marker in any sample can be mapped to a copy number of that allele. Summing the inferred copy numbers over both alleles give us, Pg. 2).

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Supplemental Box

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Claims 6, 11, 20, 23-25, and 29 lack an inventive step under PCT Article 33(3) as being obvious over Wang et al. (hereafter Wang) in view of Good Start Genetics Inc. (hereafter Good Start).

Regarding claim 6, Wang discloses the method of claim 4. However, Wang fails to disclose wherein said normalized read counts for said at least one control diploid locus are obtained from a synthetic nucleic acid.
Good Start is in the field of multiplex analyses for genetic loci (Abstract) and teaches wherein said normalized read counts for said at least one control diploid locus are obtained from a synthetic nucleic acid (it should be appreciated that probes, primers, and other nucleic acids designed or used herein may be synthetic, Pg. 72, Lns. 4-5).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the nucleic acids of Good Start. The motivation would have been to use suitable nucleic acids to determine copy number (Pg. 72, Lns. 23-29).

Regarding claim 11, Wang discloses the method of claim 1. However, Wang fails to disclose wherein said sequencing step comprises a Sanger sequencing method or a next-generation sequencing method.
Good Start is in the field of multiplex analyses for genetic loci (Abstract) and teaches wherein said sequencing step comprises a Sanger sequencing method or a next-generation sequencing method (Next-generation sequencing may ba used to quantitatively measure the abundance of each isolated target nucleic acid obtained, Pg. 23, Lns. 5-6).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the sequencing method of Good Start. The motivation would have been to effectively measure the abundance of isolated nucleic acids (Pg. 23, Lns. 5-6).

Regarding claim 20, Wang discloses the method of claim 19. However, Wang fails to disclose wherein said disease is spinal muscular atrophy.
Good Start is in the field of multiplex analyses for genetic loci (Abstract) and teaches wherein said disease is spinal muscular atrophy (in some embodiments, the methods disclosed herein are useful for diagnosis of one or more heritable disorders . . . In some embodiments, the heritable disorders are selected from: . . . Spinal Muscular Atrophy (SMN1)-SMA, Pg. 30-31, Lns. 19-6).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the disease of Good Start. The motivation would have been to diagnose the desired heritable disorder (Pg. 30-31, Lns. 19-6).

Regarding claim 23, modified Wang discloses the method of claim 14. However Wang fails to disclose further comprising determining carrier status for spinal muscular atrophy.
Good Start is in the field of multiplex analyses for genetic loci (Abstract) and teaches further comprising determining carrier status for spinal muscular atrophy (in some embodiments, the methods disclosed herein are useful for diagnosis of one or more heritable disorders . . . In some embodiments, the heritable disorders are selected from: . . . Spinal Muscular Atrophy (SMN1)-SMA, Pg. 30-31, Lns. 19-6).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the disease of Good Start. The motivation would have been to diagnose the desired heritable disorder (Pg. 30-31, Lns. 19-6).

Regarding claim 24, modified Wang discloses the method of claim 23. However, Wang fails to disclose further comprising determining carrier status for at least one other autosomal recessive trait.
Good Start is in the field of multiplex analyses for genetic loci (Abstract) and teaches further comprising determining carrier status for at least one other autosomal recessive trait (in some embodiments, the methods disclosed herein are useful for diagnosis of one or more heritable disorders . . . In some embodiments, the heritable disorders are selected from: . . . ABCC8-Related Hyperinsulinism; . . . Bloom's Syndrome; Canavan Disease; CFTR-Related Disorders-cystic fibrosis; . . . Familial Dysautonomia; Fanconi Anemia-FANCC; . . . Maple Syrup Urine Disease; . . . Nieman-Pick Type A-Acid Sphingomyelinase Deficiency; . . . Spinal Muscular Atrophy (SMN1)-SMA; Tay Sachs-HexA Deficiency, Pg. 30-31, Lns. 19-6).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the diseases of Good Start. The motivation would have been to diagnose the desired heritable disorder (Pg. 30-31, Lns. 19-6).

Regarding claim 25, modified Wang discloses the method of claim 24. Good Start further discloses wherein said at least one other autosomal recessive trait is selected from cystic fibrosis, sickle cell anemia, tay sachs disease, Familial hyperinsulinism, Canavan Disease, Maple Syrup Urine Disease, Bloom's Syndrome, Usher Syndrome type IIIA, Dihydrolipoamide dehydrogenase deficiency, Fanconi anemia group C, Familial dysautonomia, Mucolipidosis Type IV, Usher Syndrome Type IV, Nieman-Pick disease type A/B, Walker Warburg syndrome, and Joubert Syndrome (in some embodiments, the methods disclosed herein are useful for diagnosis of one or more heritable disorders . . . In some embodiments, the heritable disorders are selected from: . . . ABCC8-Related Hyperinsulinism; . . . Bloom's Syndrome; Canavan Disease; CFTR-Related Disorders-cystic fibrosis; . . . Familial Dysautonomia; Fanconi Anemia-FANCC; . . . Maple Syrup Urine Disease; . . . Nieman-Pick Type A-Acid Sphingomyelinase Deficiency; . . . Spinal Muscular Atrophy (SMN1)-SMA; Tay Sachs-HexA Deficiency, Pg. 30-31, Lns. 19-6).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the diseases of Good Start. The motivation would have been to diagnose the desired heritable disorder (Pg. 30-31, Lns. 19-6).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

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Regarding claim 29, Wang discloses the method of claim 26. However, Wang fails to disclose wherein said first and second loci are implicated in an autosomal recessive disorder.
Good Start is in the field of multiplex analyses for genetic loci (Abstract) and teaches wherein said first and second loci are implicated in an autosomal recessive disorder (according to some aspects, the disclosure relates to multiplex diagnostic methods. In some embodiments, multiplex diagnostic methods comprise capturing a plurality of genetic loci in parallel, Pg. 31, Lns. 15-17).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the disease of Good Start. The motivation would have been to diagnose the desired heritable disorder (Pg. 30-31, Lns. 19-6).

Claims 8, 9, 15, 21, and 30 lack an inventive step under PCT Article 33(3) as being obvious over Wang et al. (hereafter Wang) in view of Bhattacharyya et al. (hereafter Bhattacharyya).

Regarding claim 8, Wang discloses the method of claim 7. However, Wang fails to disclose wherein said first gene is SMN1 and said second gene is SMN2.
Bhattacharyya is in the field of assays for use in treatment of spinal muscular atrophy (Abstract) and teaches wherein said first gene is SMN1 and said second gene is SMN2 (The SMA disease gene has been mapped by linkage analysis to a complex region of chromosome 5q. In humans, this region has a large inverted duplication; consequently, there are two copies of the SMN gene. SMA is caused by a mutation or deletion of the telomeric copy of the gene (SMN1) in both chromosomes, resulting in the loss of SMN1 gene function. However, all patients retain a centromeric copy of the gene (SMN2), and its copy number in SMA patients has been implicated as having an important modifying effect on disease severity, Col. 2, Lns. 10-20).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the target genes of Bhattacharrya. The motivation would have been to identify the carrier status of an individual for Spinal Muscular Atrophy (Col. 1, Lns. 19-26).

Regarding claim 9, Wang discloses the method of claim 8. However, Wang fails to disclose further comprising the step of diagnosing a carrier phenotype for spinal muscular atrophy.
Bhattacharyya is in the field of assays for use in treatment of spinal muscular atrophy (Abstract) and teaches further comprising the step of diagnosing a carrier phenotype for spinal muscular atrophy (The SMA disease gene has been mapped by linkage analysis to a complex region of chromosome 5q. In humans, this region has a large inverted duplication; consequently, there are two copies of the SMN gene. SMA is caused by a mutation or deletion of the telomeric copy of the gene (SMN1) in both chromosomes, resulting in the loss of SMN1 gene function. However, all patients retain a centromeric copy of the gene (SMN2), and its copy number in SMA patients has been implicated as having an important modifying effect on disease severity, Col. 2, Lns. 10-20).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the target genes of Bhattacharrya. The motivation would have been to identify the carrier status of an individual for Spinal Muscular Atrophy (Col. 1, Lns. 19-26).

Regarding claim 15, Wang discloses the method of claim 14. However, Wang fails to disclose wherein said first genetic locus is SMN1 and said second genetic locus is SMN2.
Bhattacharyya is in the field of assays for use in treatment of spinal muscular atrophy (Abstract) and teaches wherein said first genetic locus is SMN1 and said second genetic locus is SMN2 (The SMA disease gene has been mapped by linkage analysis to a complex region of chromosome 5q. In humans, this region has a large inverted duplication; consequently, there are two copies of the SMN gene. SMA is caused by a mutation or deletion of the telomeric copy of the gene (SMN1) in both chromosomes, resulting in the loss of SMN1 gene function. However, all patients retain a centromeric copy of the gene (SMN2), and its copy number in SMA patients has been implicated as having an important modifying effect on disease severity, Col. 2, Lns. 10-20).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the target genes of Bhattacharrya. The motivation would have been to identify the carrier status of an individual for Spinal Muscular Atrophy (Col. 1, Lns. 19-26).

Regarding claim 21, Wang discloses the method of claim 19. However, Wang fails to disclose wherein said loci are selected from SMN1, SMN2 and loci different from SMN1 and SMN2.
Bhattacharyya is in the field of assays for use in treatment of spinal muscular atrophy (Abstract) and teaches wherein said loci are selected from SMN1, SMN2 and loci different from SMN1 and SMN2 (The SMA disease gene has been mapped by linkage analysis to a complex region of chromosome 5q. In humans, this region has a large inverted duplication; consequently, there are two copies of the SMN gene. SMA is caused by a mutation or deletion of the telomeric copy of the gene (SMN1) in both chromosomes, resulting in the loss of SMN1 gene function. However, all patients retain a centromeric copy of the gene (SMN2), and its copy number in SMA patients has been implicated as having an important modifying effect on disease severity, Col. 2, Lns. 10-20).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the target genes of Bhattacharrya. The motivation would have been to identify the carrier status of an individual for Spinal Muscular Atrophy (Col. 1, Lns. 19-26).

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INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

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Regarding claim 30, Wang discloses the method of claim 29. However, Wang fails to disclose wherein said first locus is SMN1 and said second locus is SMN2.
Bhattacharyya is in the field of assays for use in treatment of spinal muscular atrophy (Abstract) and teaches wherein said first locus is SMN1 and said second locus is SMN2 (The SMA disease gene has been mapped by linkage analysis to a complex region of chromosome 5q. In humans, this region has a large inverted duplication; consequently, there are two copies of the SMN gene. SMA is caused by a mutation or deletion of the telomeric copy of the gene (SMN1) in both chromosomes, resulting in the loss of SMN1 gene function. However, all patients retain a centromeric copy of the gene (SMN2), and its copy number in SMA patients has been implicated as having an important modifying effect on disease severity, Col. 2, Lns. 10-20).
It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the method of determining copy number state of Wang and the target genes of Bhattacharrya. The motivation would have been to identify the carrier status of an individual for Spinal Muscular Atrophy (Col. 1, Lns. 19-26).

Claims 1-31 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-010/01WO	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2013/032885**	International filing date *(day/month/year)* **19 March 2013 (19.03.2013)**	(Earliest) Priority Date *(day/month/year)* 09 April 2012 (09.04.2012)

Applicant

GOOD START GENETICS, INC.

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 9
      ☐ as suggested by the applicant.
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figure is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/032885

A. CLASSIFICATION OF SUBJECT MATTER

G06F 19/28(2011.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G06F 19/28; C40B 30/00; G06F 19/00; C40B 50/02; G06F 19/18; G06F 17/30; G06F 19/22; C12Q 1/68

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords:genetic, test, variant, data, mutation, information

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011-0034342 A1 (RICHARD FOX) 10 February 2011 See paragraphs [0015], [0035], [0040], [0119], [0165], [0173], [0178]; and fig. 1.	1,3,11,13
A		2,4-10,12,14-40
Y	US 2002-0187496 A1 (LEIF ANDERSSON et al.) 12 December 2002 See paragraphs [0003]-[0004], [0006], [0023], [0030], [0032], [0041], [0047], [0052], [0060], [0062], [0075], [0078], [0080]; and figs. 1-2, 4-6, 10-11.	1,3,11,13
A	EP 2437191 A2 (GENE SECURITY NETWORK LLC) 04 April 2012 See paragraphs [0002], [0024]-[0050]; and fig. 19.	1-40
A	WO 2002-093453 A2 (X-MINE, INC.) 21 November 2002 See paragraphs [0002], [0024]-[0027]; and figs. 3A-3B.	1-40
A	WO 2010-024894 A1 (23ANDME, INC.) 04 March 2010 See paragraph [0002]; and fig. 1.	1-40

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2013 (25.06.2013)	**28 June 2013 (28.06.2013)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea	BYUN, Sung Cheal
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-8262

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/032885

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011-0034342 A1	10.02.2011	EP 2250594 A1	17.11.2010
		WO 2009-102901 A1	20.08.2009
US 2002-0187496 A1	12.12.2002	WO 2002-17207 A2	28.02.2002
		WO 2002-17207 A3	12.12.2002
EP 2437191 A2	04.04.2012	AU 2006-318425 A1	31.05.2007
		AU 2006-318425 A2	21.08.2008
		CA 2632230 A1	31.05.2007
		CN 101346724 A	14.01.2009
		EP 1960929 A2	27.08.2008
		EP 1960929 A4	28.01.2009
		JP 2009-517050 A	30.04.2009
		US 2007-0027636 A1	01.02.2007
		WO 2007-062164 A2	31.05.2007
		WO 2007-062164 A3	29.11.2007
WO 02-093453 A2	21.11.2002	AU 2002-308662 A1	25.11.2002
		AU 2002-308662 A8	25.11.2002
		WO 2009-3453 A2	21.11.2002
		WO 2009-3453 A3	11.03.2004
WO 2010-024894 A1	04.03.2010	US 2010-0057374 A1	04.03.2010
		US 2010-0057807 A1	04.03.2010
		US 8428886 B2	23.04.2013

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
TOSTI ROBERT J.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**28 June 2013 (28.06.2013)**
Applicant's or agent's file reference GSGE-010/01WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2013/032885	**19 March 2013 (19.03.2013)**	09 April 2012 (09.04.2012)

International Patent Classification (IPC) or both national classification and IPC

G06F 19/28(2011.01)i

Applicant

GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [x] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea Facsimile No. 82-42-472-7140	25 June 2013 (25.06.2013)	BYUN, Sung Cheal Telephone No. 82-42-481-8262

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2013/032885

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. a sequence listing filed or furnished
      ☐ on paper
      ☐ in electronic form

   b. time of filing or furnishing
      ☐ contained in the international application as filed.
      ☐ filed together with the international application in electronic form.
      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additioanl copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2013/032885

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-40	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	2,4-10,12,14-40	YES
	Claims	1,3,11,13	NO
Industrial applicability (IA)	Claims	1-40	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: US 2011-0034342 A1 (RICHARD FOX) 10 February 2011
D2: US 2002-0187496 A1 (LEIF ANDERSSON et al.) 12 December 2002
D3: EP 2437191 A2 (GENE SECURITY NETWORK LLC) 04 April 2012
D4: WO 2002-093453 A2 (X-MINE, INC.) 21 November 2002
D5: WO 2010-024894 A1 (23ANDME, INC.) 04 March 2010

2.1 Novelty and Inventive Step

2.1.1 Independent Claim 1 and Dependent Claims 2-10

D1, which is considered to be the closest prior art to the subject matter of claim 1, discloses a method comprising:

retrieving from one or more computer-readable storage devices a first variant object comprising a description of a first mutation as a first variant of a reference and a second variant object comprising a description of a second mutation as a second variant of the reference, each of the first and second variant objects being an instance of an abstract class of a genomic feature (retrieving from a library each variant which describe properties of molecular variants, see paragraphs [0119], [0165] and fig. 1 in D1);

determining a relationship between the first and second mutations (determining mutations and establishing relationships between the mutations, see paragraphs [0050], [0118] and fig. 1 in D1);

retrieving a third object comprising a description of the relationship, the third object also being an instance of the abstract class (receiving a data set of mutations which established relationships between the various members of the data, see paragraphs [0050], [0165] and fig. 1

Continued on Supplemental Box

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2013/032885

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

In claim 4, the term "the memory" has not been previously defined. Therefore, claim 4 is not clear, contrary to the requirement of PCT Article 6.

In claims 8 and 18, the term "the information" has not been previously defined. Therefore, claims 8 and 18 are not clear, contrary to the requirement of PCT Article 6.

In claim 24, the term "the one or more computer-readable storage devices" has not been previously defined. Therefore, claim 24 is not clear, contrary to the requirement of PCT Article 6.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of : Box No. V

in D1); and

providing a description of the variant based on the third object (describing properties of the molecular variants of objective data, see paragraph [0119] and fig. 1 in D1).

The subject matter of claim 1 differs from that of D1 in that claim 1 comprises the feature of receiving genetic data relating to an individual, the data representing at least a first mutation and a second mutation. However, this feature can readily be predicted from D2 that discloses the feature of obtaining genetic information about sequence variants from the sampled individuals' information (see paragraphs [0006], [0030], [0041] and figs. 1-2, 4 in D2). Accordingly, claim 1 would have been obvious over D1 in view of D2. Therefore, claim 1 lacks an inventive step under PCT Article 33(3).

The additional feature (the one or more computer-readable storage devices comprise a relational database) of claim 3 dependent on claim 1 can readily be predicted from D1 that discloses the feature of one computer comprising a database capable of storing relationships between the data (see paragraphs [0050], [0199] and fig. 1 in D1). Accordingly, claim 3 would have been obvious over D1 in view of D2. Therefore, claim 3 lacks an inventive step under PCT Article 33(3).

The additional features of claims 2 and 4-10 directly or indirectly dependent on claim 1 are not disclosed in any of the prior art documents, nor are they obvious to a person skilled in the art over the documents. Accordingly, claims 2 and 4-10 are novel and involve an inventive step under PCT Article 33(2) and (3).

2.1.2 Independent Claim 11 and Dependent Claims 12-20

The features of independent claim 11 essentially correspond to those of claim 1, except for the category of the invention and an added feature of a processor (a processor, see paragraph [0078] and fig. 11 in D2). Therefore, for the same reasons as those of claim 1, claim 11 lacks an inventive step under PCT Article 33(3).

The additional feature (the database is a relational database) of claim 13 dependent on claim 11, can readily be predicted from D2 that discloses the feature of a relationship between database objects (see paragraph [0023] and fig. 2 in D2). Accordingly, claim 13 would have been obvious over D1 in view of D2. Therefore, claim 13 lacks an inventive step under PCT

Continued on The Next Page

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Previous Page

Article 33(3).

The additional features of claims 12 and 14-20 directly or indirectly dependent on claim 11 are not disclosed in any of the prior art documents, nor are they obvious to a person skilled in the art over the documents. Accordingly, claims 12 and 14-20 are novel and involve an inventive step under PCT Article 33(2) and (3).

2.1.3 Independent Claim 21 and Dependent Claims 22-30

The subject matter of claim 21 differs from these prior art documents in that a method in claim 21 comprises: providing, using a computer comprising a memory coupled to a processor, code describing an abstract class of genomic feature object and creating relation objects, each relation object being an instance of the genomic feature object and comprising one or more genomic feature objects and description of a relationship among the one or more genomic feature objects. And it is not obvious to a person skilled in the art over the documents taken alone or in combination. Therefore, claim 21 meets the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

Claims 22-30 are dependent on claim 21 and therefore meet the requirements of PCT Article 33(2) and (3).

2.1.4 Independent Claim 31 and Dependent Claims 32-40

The features of independent claim 31 essentially correspond to those of claim 21, except for the category of the invention and an added feature of a processor (see paragraph [0078] and fig. 11 in D2). Therefore, for the same reasons as those of claim 21, claim 31 meets the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

Claims 32-40 are dependent on claim 31 and therefore meet the requirements of PCT Article 33(2) and (3).

2.2 Industrial Applicability

Claims 1-40 are industrially applicable under PCT Article 33(4).

ENTERED IN CPI

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: Thomas C. Meyers
Brown Rudnick LLP
One Financial Center
Boston, MA 02111
United States of America

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing (day/month/year) 18 MAR 2015
Applicant's or agent's file reference GSGE-017/01WO 29258/86	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US14/40516	International filing date (day/month/year) 02 June 2014 (02.06.2014)
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
   - ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.
   - ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2014)

18 MAR 2015

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-017/01WO 29258/86	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US14/40516	International filing date *(day/month/year)* 02 June 2014 (02.06.2014)	(Earliest) Priority Date *(day/month/year)* 03 June 2013 (03.06.2013)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established by this Authority to read as follows:

STORING SEQUENCE READ DATA

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the drawings to be published with the abstract is Figure No. 7
      ☐ as suggested by the applicant.
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/40516

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G06F 19/22; C12N 15/09 (2014.01)
CPC - C12Q 1/6869; G06F 19/22, 17/30985
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) Classification(s): G06F 19/22; C12N 15/09; C12Q 1/68 (2014.01)
CPC Classification(s): C12Q 1/6869; G06F 19/22, 17/30985

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C, B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; IEEE/IEEEXplore; Google/Google Scholar; KEYWORDS: duplicate, sequence, identify, sample, set, store

C. DOCUMENTS CONSIDERED TO BE RELEVANT

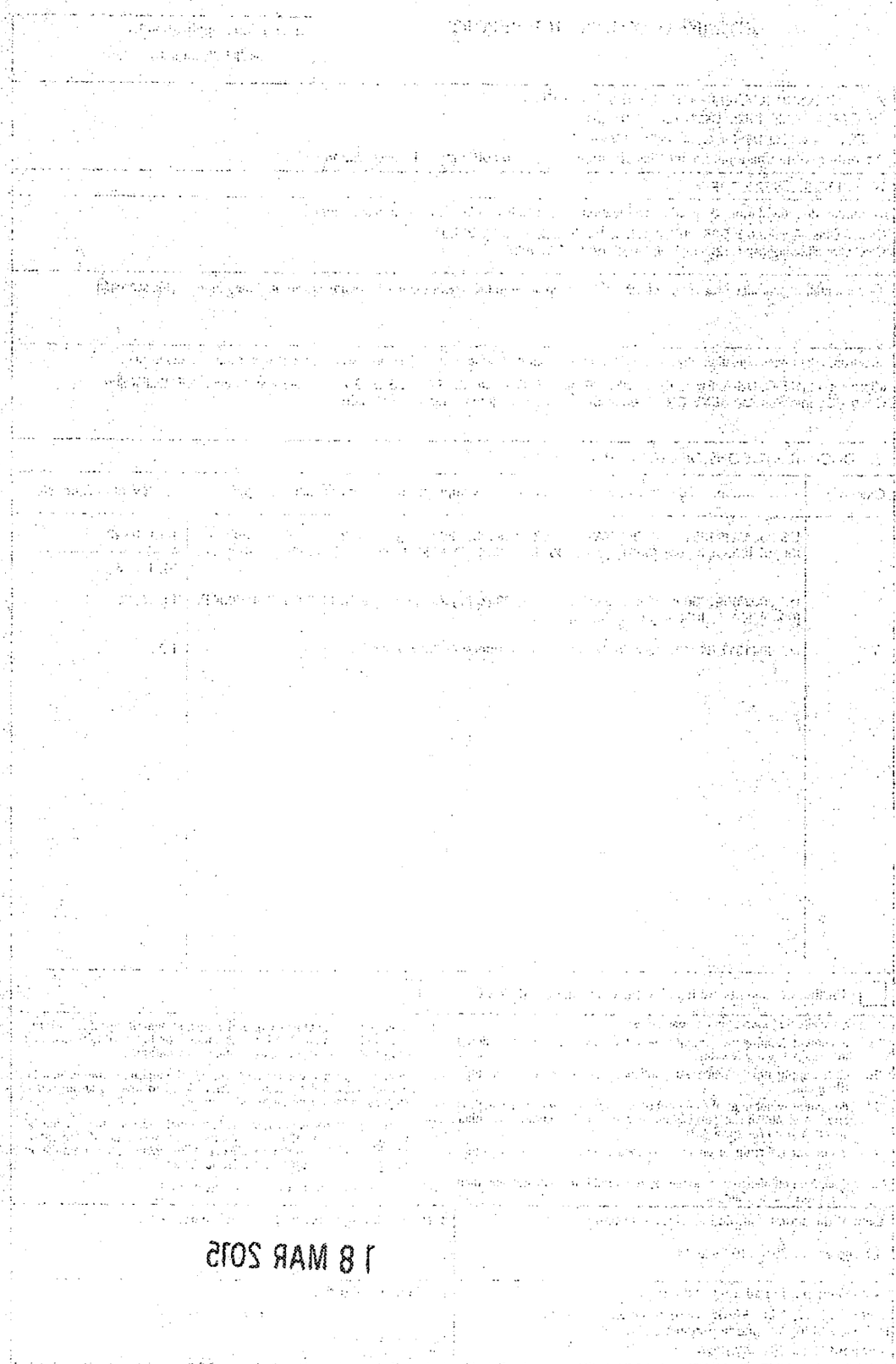
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	US 2004/0171051 A1 (HOLLOWAY, J) 02 September 2004; Figures 1, 2, 7, 8A; Paragraphs [0030], [0031], [0054], [0061], [0062], [0112], [0118], [0127]-[0129], [0133], [0150], [0154], [0212]	1-13, 16-22 — 14, 15, 23
Y	US 2002/0091666 A1 (RICE, J et al.) 11 July 2002; Figure 1; Paragraphs [0030], [0034], [0041], [0049], [0056], [0059], [0060], [0070]-[0072]	14, 15, 23
A	US 6941317 B1 (CHAMBERLIN, S et al.) 06 September 2005; entire document	1-23

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2014 (19.09.2014)	18 MAR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)


18 MAR 2015

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Thomas C. Meyers
Brown Rudnick LLP
One Financial Center
Boston, MA 02111
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	18 MAR 2015
Applicant's or agent's file reference GSGE-017/01WO 29258/86	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US14/40516	02 June 2014 (02.06.2014)	03 June 2013 (03.06.2013)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G06F 19/22; C12N 15/09 (2014.01)
CPC - C12Q 1/6869; G06F 19/22, 17/30985

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to th IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	19 September 2014 (19.09.2014)	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

18 MAR 2015

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/40516

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/40516

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	14, 15, 23	YES
	Claims	1-13, 16-22	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-23	NO
Industrial applicability (IA)	Claims	1-23	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-13, and 16-22 lack novelty under PCT Article 33(2) as being anticipated by US 2004/0171051 A1 (HOLLOWAY).

As per claim 1, Holloway discloses a method for storing sequence read data (building a master DNA sequence file 107 in maintained databases; Abstract; Figure 1; Paragraph [0030]), the method comprising: obtaining a plurality of sequence reads from a sample (assembling tag representations of DNA fragments (sequence reads) from DNA sequence files in a target domain of DNA sequence files (a sample); Paragraphs [0062], [0133], [0212]); identifying one or more sets of duplicative sequence reads within the plurality of sequence reads (identifying identical matches (duplicative sequence reads) by searching for tag matches (sequence reads); Figure 8A; Paragraphs [0112], [0118], [0127]); and storing only one sequence read from each of the one or more sets of duplicative sequence reads (a single sequence designated by a tag (one sequence read) is stored on the data file from matched pairs of tags; Paragraph [0154]).

As per claim 2, Holloway discloses the method according to claim 1. Holloway additionally discloses, wherein obtaining the plurality of sequence reads comprises sequencing a nucleic acid from the sample to generate the plurality of sequence reads (a sequencer program obtains query sequences from DNA (sequencing a nucleic acid) in the target domain (sample) to construct a list of tags (sequence reads); Paragraphs [0030], [0061], [0212]).

As per claim 3, Holloway discloses the method according to claim 2. Holloway additionally discloses, wherein sequencing comprises one selected from the group consisting of single molecule sequencing and sequencing by synthesis (the sequencing process builds complete genes by merging spliced information from assembled tags, or ESTs, and cDNA molecules (sequencing by synthesis); Paragraph [0161]).

As per claim 4, Holloway discloses the method according to claim 1. Holloway additionally discloses, wherein the sample comprises a human tissue or bodily fluid sample (the target domain (sample) includes a combination of DNA sequence files from public human genome databases and cell samples (human tissue); Paragraphs [0030], [0212]).

As per claim 5, Holloway discloses the method according to claim 1. Holloway additionally discloses, wherein obtaining the plurality of sequence reads comprises obtaining a computer-readable input file (the sequence data from which tags are constructed (sequence reads) is read in FastA format by a computer program (computer-readable input file); Paragraph [0034]).

As per claim 6, Holloway discloses the method according to claim 5. Holloway additionally discloses wherein the computer-readable input file is once selected from the group consisting of: a FASTA file; a FASTQ file; and a VCF file (the DNA file read by the computer program is in FastA format; Paragraph [0034]).

As per claim 7, Holloway discloses the method according to claim 1. Holloway additionally discloses, further comprising storing the only one sequence read from each of the one or more sets of duplicative sequence reads in at least one master sequence read file (a single sequence designated by a tag (one sequence read) from matched pairs of tags is stored in master DNA sequence data file 107; Figure 1; Paragraphs [0030], [0154]).

As per claim 8, Holloway discloses the method according to claim 7. Holloway additionally discloses, wherein the at least one master sequence read file is a text file (the algorithm works on text strings in base characters and writes to file in FastA, a text-based format (a text file); Paragraphs [0034], [0058]).

As per claim 9, Holloway discloses the method according to claim 7. Holloway additionally discloses, further comprising collecting meta information for each of the plurality of sequence reads and matching the meta information to a single read in the at least one master sequence read file (storing tag position value 805 (meta information) in the data structure for each tag and used to find identity (matching the meta information) with a DNA subsequence (single read) in the database file (master sequence); Paragraph [0061]).

As per claim 10, Holloway discloses the method according to claim 9. Holloway additionally discloses, wherein the meta information comprises a sequence read ID (additional information in the tag data structure records includes a sequence ID 803; Figure 7; Paragraph [0061]).

-***-Continued Within the Next Supplemental Box-***-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/40516

Supplemental Box

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Continuation of:

-***-Continued from Box V: Citations and Explanations-***-

As per claim 11, Holloway discloses the method according to claim 9. Holloway additionally discloses, wherein the obtaining, identifying, and storing steps (the steps constructing tags (obtaining), finding matches (identifying), and storing to file; Figure 4) are performed by a computer comprising a processor coupled to a non-transitory memory (of a computer system having a CPU 207 coupled to memory 209; Figure 2; Paragraphs [0031], [0127]), and further wherein the collected and matched meta information is stored in a computer-readable output file (the position and sequence identifiers used for matching is stored and written in a data file record, in FastA format (a computer-readable output file); Figure 3; Paragraphs [0034], [0061]).

As per claim 12, Holloway discloses the method according to claim 7. Holloway additionally discloses, wherein sequence reads are stored in the at least one master sequence read file using IUPAC nucleotide characters (text string representations of DNA fragments used to build the master DNA sequence file are written using the alphabet A, C, G, and T (IUPAC nucleotide characters); Paragraphs [0030], [0034], [0062]).

As per claim 13, Holloway discloses the method according to claim 11. Holloway additionally discloses, wherein the sequence reads are stored in the at least one master sequence read file using IUPAC nucleotide characters (text string representations of DNA fragments used to build the master DNA sequence file are written using characters A, C, G, and T (IUPAC nucleotide characters); Paragraphs [0030], [0034], [0062]).

As per claim 16, Holloway discloses a system for storing for storing sequence read data (maintaining a database for building a master DNA sequence file 107; Abstract; Figure 1; Paragraph [0030]), the system comprising: a processor coupled to a non-transitory memory containing instructions executable by the processor (a computer system having CPU 207 (processor) coupled to memory 209 storing computer program 221 (instructions) executed by the CPU; Figure 2; Paragraphs [0031], [0150]) to cause the system to: obtain input file comprising a plurality of sequence reads (to read a file containing sequences of DNA to compute tags (sequence reads); Paragraph [0127]), identify one or more sets of duplicative sequence reads within the plurality of sequence reads (identifying matches (duplicative sequence reads) by searching tags (sequence reads) generated from the DNA sequence file; Figure 8A; Paragraphs [0112], [0118]), and store only one of the sequence reads from each of the one or more sets of duplicative sequence reads (a single sequence designated by a tag (one sequence read) is stored on the data file from matched pairs of tags; Paragraph [0154]).

As per claim 17, Holloway discloses the system of claim 16. Holloway additionally discloses, further comprising a nucleic acid sequencing instrument connected to the system (generating sequence files from a DNA sequencer program (instrument) running on general purpose computer 225 (connected to the system); Figure 2; Paragraphs [0030], [0031]).

As per claim 18, Holloway discloses the system of claim 16. Holloway additionally discloses, wherein the system is operable to store the only one of the sequence reads from each of the one or more sets of duplicative reads in a text file using IUPAC nucleotide characters (a single sequence designated by a tag is stored (one sequence read) from matched pairs of tags (duplicative reads) to a data file consisting of simple text strings from the alphabet A, C, G, and T (IUPAC nucleotide characters); Figure 1; Paragraphs [0030], [0034], [0154]).

As per claim 19, Holloway discloses a method for compressing sequence data (reducing redundancy (compressing) in analyzed sequences; Paragraph [0054]), the method comprising: obtaining, using a computer system comprising a processor coupled to a non-transitory memory, a plurality of sequence reads (reading, by a computer system having a CPU 207 (processor) coupled to memory 209, DNA sequences to compute tags (reads); Figure 2; Paragraphs [0031], [0127]), each sequence read comprising a sequence string and meta information (formatting a tag data structure with the tag value 801 (sequence string) followed by its position 805 (meta information); Figure 7; Paragraph [0061]); identifying a subset of the sequence strings that contains only unique entries (sorting by length to find the longest sequences 1201 (identifying a subset) of the DNA sequences previously unused (contains only unique entries); Paragraph [0128]); writing output comprising the subset and--for each of the plurality of sequence reads--the meta information for that sequence read with an indicator of the unique entry in the subset that represents that sequence read (allowing specific annotations (writing output), in the represented clusters (subset), for their members (sequence reads) using position (meta) information relative to the longest sequence assigned the cluster identifier (an indicator of the unique entry in the subset) maintained to annotate and merge members; Paragraphs [0128]-[0130]).

As per claim 20, Holloway discloses the method of claim 19, wherein the output comprises one or more text files that store the subset using IUPAC nucleotide codes (the union of elements (output) replaces matched pairs on a data file (text file) containing the single sequence (subset) in FastA format consisting of the alphabet A, C, G, and T (IUPAC nucleotide codes); Paragraphs [0034], [0154]).

As per claim 21, Holloway discloses the method of claim 20. Holloway additionally discloses, further comprising processing the output to create new FASTA or FASTQ files comprising the plurality of sequence reads (new query sequences are incrementally written in FastA files as new human genomic DNA sequence data are generated (sequence reads); Paragraphs [0034], [0129]).

As per claim 22, Holloway discloses the method of claim 21. Holloway additionally discloses, wherein the plurality of sequence reads are obtained as FASTA or FASTQ files (new data generated is read by the program in FastA format; Paragraphs [0034], [0129]) and the new FASTA or FASTQ files contain the same information as the FASTA or FASTQ files (using clustering with the sequence files derived from the newly generated data, output files are processed and written in FastA format (the same information) to an updated master sequence file; Figure 1; Paragraphs [0034], [0129]).

-***-Continued Within the Next Supplemental Box-***-

Supplemental Box

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-***-Continued from Previous Supplemental Box-***-

Claims 14, 15, and 23 lack an inventive step under PCT Article 33(3) as being obvious over Holloway in view of US 2002/0091666 A1, to RICE et al. (hereinafter 'Rice').

As per claim 14, Holloway discloses the method of claim 13. Holloway additionally discloses, wherein the at least one master sequence read file and the output file are stored as plain text files (the master DNA sequence file 107 and output sequence reports 111 generated from the sequencer program are written in the text-based format FastA (plain text files); Paragraphs [0030], [0034]). Holloway does not disclose, and further wherein the computer system comprises a text editor program capable of opening the plain text files. Rice discloses, and further wherein the computer system comprises a text editor program capable of opening the plain text files (computer system 10 includes standard, POSIX text-editing tools like diff (a text editor program) to comparing differences in text on a character-by-character basis and displayed on a terminal; Figure 1; Paragraphs [0049],[0056], [0059], [0060]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to modify the method of Holloway with the teaching of Rice, because by doing so, the method of Holloway would provide textual displays representing a comparison between processed text files using a standard text-editing tool.

As per claim 15, Holloway discloses the method of claim 14. Holloway does not disclose, wherein the text editor program is capable of displaying the plain text files on a computer screen, showing the meta information and the sequence reads in a human-readable format. Rice discloses, wherein the text editor program is capable of displaying the plain text files on a computer screen (a text-editing tool (text editor program) compares text in a character-by-character basis on a display terminal; Paragraphs [0049],[0056],[0059]), showing the meta information and the sequence reads in a human-readable format (for representing an overlay in the meta-language XML for representing structured information about samples (meta information) and DNA arrays (sequence reads) in a flexible format (human-readable format); Paragraphs [0038], [0060], [0070]-[0072]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to modify the method of Holloway with the teaching of Rice, because by doing so, the method of Holloway would provide a representation on end user displays of models in a DNA array experiment using the flexible XML framework.

As per claim 23, Holloway discloses the method of claim 19. Holloway does not disclose, wherein the output occupies less than 25% of the disk space required to store the obtained plurality of sequence reads. Rice discloses wherein the output occupies less than 25% of the disk space required to store the obtained plurality of sequence reads (the mean storage requirement after analysis is one-tenth (less than 25%) when compared to the storage requirement for a complete model sequence (to store the obtained plurality of sequence reads); Paragraphs [0041], [0042]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to modify the method of Holloway with the teaching of Rice, because by doing so, the method of Holloway would provide additional savings in storage space by using more compact representations of the computational models of DNA sequence data.

Claims 1-23 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PCT Recordation of Search History

Case/PCT Application Number: PCT/US14/40516

CLIN Number/Technical Field of PCT Application: 7

Date(s) during which the search was conducted: 11 September 2014 - 19 September 2014

Date of Completion of Recordation of Search History Form: 19 September 2014

Research Analyst Initials: NJH

Search Approval Official (SAO) Initials: HKP

Field of Search/Classification Information:

IPC(8) Classification(s): G06F 19/22; C12N 15/09; C12Q 1/68 (2014.01)

CPC Classification(s): C12Q 1/6869; G06F 19/22, 17/30985

Database(s) Searched (Patent and Non-Patent Literature (NPL), Including Sub-Databases and Files Searched) and Search Terms Used:

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C, B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; IEEE/IEEEXplore; Google/Google Scholar;

KEYWORDS: duplicat*, sequenc*, identify*, sampl*, set*, store*

Database Search String Recordation, Including Dates of Searches):
Patent Database Search Strategy/Results:

#	results	criteria		last run
23	29 hits	Combined query	(12 AND 22) NOT 18	9/17/2014
22	319 hits	Combined query	20 AND 21	9/17/2014
21	2093 hits	Full patent spec.	((DNA OR nucle* OR gen*) ADJ4 (sequen* OR string*)) NEAR10 compress*	9/17/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
20	136954 hits	Claims, Title or Abstract	(duplicat* OR identic* OR match* OR *4uniqu*) AND (sequenc* OR string*) AND (identif* OR find* OR detect* OR extract* OR parsu*)	9/17/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
19	5 hits	Combined query	(4 OR 5 OR 6) AND 18	9/17/2014
18	282 hits	Combined query	17 NOT (15 OR 8)	9/17/2014
17	285 hits	Combined query	12 AND 16	9/17/2014
16	433 hits	Full patent spec.	((DNA OR nucle*) ADJ4 (sequen* OR string*)) NEAR10 compress*	9/17/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
15	115 hits	Combined query	(4 AND 14) NOT 8	9/17/2014
14	51476 hits	Combined query	12 AND 13	9/17/2014
13	5088048 hits	Full patent spec.	(reduc* OR compress* OR lower* OR minimiz*) NEAR20 (spac* OR storag* OR siz* OR volum*)	9/17/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	

#	results		criteria	mark
12	401283 hits	Combined query	9 OR 10 OR 11	9/15/2014
11	237796 hits	Any Classification	C12Q0/00168	9/15/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
10	254052 hits	Any Classification	C12N001509	9/15/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
9	3404 hits	Any Classification	G06F001922	9/15/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
8	134 hits	Combined query	5 AND 7	9/15/2014

7	61473 hits	Full patent spec	[FASTA OR FASTQ OR VCF OR IUPAC] AND ([reduc* OR remov* OR compress* OR (de ADJ duplicat*)] NEAR30 (file* OR sequenc* OR data)]	9/15/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
6	8855 hits	Title or Abstract	[duplicat* OR identic* OR match*] AND [sequenc* OR string*] AND [identif* OR find* OR detect*]	9/15/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
5	13928 hits	Title or Abstract	[duplicat* OR repet* OR repeat* OR identic* OR match* OR copy OR copies OR redundan*] AND [sequenc* OR string*1 OR array*1 OR code] AND [identif* OR locat* OR find* OR detect*] AND [obtain* OR read* OR extract* OR pars* OR retriev*]	9/15/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
4	16508 hits	Title or Abstract	[duplicat* OR repet* OR repeat* OR identic* OR match* OR copy OR copies OR redundan*] AND [sequenc* OR string*1 OR array*1 OR characters OR chars OR letters OR code] AND [identif* OR locat* OR find* OR match* OR detect* OR align* OR search*] AND [obtain* OR read* OR extract* OR sampl* OR pars* OR retriev*] AND [stor* OR sav* OR writ* OR cop*]	9/15/2014
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
3	9 hits	Assignee/Applicant	GOOD START GENETIC*	9/15/2014
		Claims, Title or Abstract	sequen* AND [duplicat* OR redundan* OR match* OR identic*]	
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
2	30 hits	Assignee/Applicant	GOOD START GENETIC*	9/15/2014
		Claims, Title or Abstract	sequen*	
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	
1	12 hits	Claims, Title or Abstract	sequen*	9/15/2014
		Inventor(s)	[KENNEDY NEAR2 Caleb] OR [CHENNAGIRI NEAR2 Nira]	
		Databases	USG USA EPA EPB WO JP DEG DEA DET DEU GBA FRA	
		Years	1836-2014	

ProQuest:
11 September 2014

Set	Search	Databases	Results
S4	⊟ cpc("G06F 17/30985") AND ab(duplicat*) AND ab(sequen*) **Databases:** Derwent World Patents Index® European Patents Fulltext INPADOC / Family and Legal Status	3 databases	5
S3	⊟ cpc("G06F 19/22") AND pab(duplicat*) AND pab(sequen*) **Databases:** Derwent World Patents Index® European Patents Fulltext INPADOC / Family and Legal Status	3 databases	14
S2	⊟ cpc("G06F 19/22") AND duplicat* AND sequen* **Databases:** Derwent World Patents Index® European Patents Fulltext INPADOC / Family and Legal Status	3 databases	121
S1	⊟ cpc("C12Q 1/6869") AND duplicat* AND match* AND compress* **Databases:** Derwent World Patents Index® European Patents Fulltext INPADOC / Family and Legal Status	3 databases	13

Non-Patent Literature (NPL) Search Strategy/Results:

ProQuest:
11 September 2014

- ((remov* OR identif*) NEAR/4 (duplicat* OR redundan*)) AND DNA AND sequen*
- compress* AND format* AND sequen* AND duplicat* AND extract*
- (deduplicat* NEAR/10 (identic* OR match* OR sam*)) AND (char* NEAR/10 seq*)

Google/Google Scholar:
11 September 2014

- identify duplicate sequence portions from sample
- merge duplicate string sequence from nucleotide sample
- bioinformatic detect matching sequence reads

IEEE/IEEEXplore:
11 September 2014

- ((remov* OR dedup*) <near/10> (match* OR cop*)) AND sequenc*
- ((find* OR identif*) <near/20> (segmen* OR portion*)) AND sequen* AND DNA
- (string* AND pattern* AND match*) <near/30> sequenc*

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-031/01WO 29258/153	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2016/013346**	International filing date *(day/month/year)* **14 January 2016 (14.01.2016)**	(Earliest) Priority Date *(day/month/year)* 15 January 2015 (15.01.2015)
Applicant **GOOD START GENETICS, INC.**		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **4** sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/013346

A. CLASSIFICATION OF SUBJECT MATTER

C12Q 1/68(2006.01)i, G06F 19/22(2011.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q 1/68; C12N 15/11; G06F 19/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: FAST-SeqS, single nucleotide polymorphism (SNP), pre-implantation genetic screening

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KINDE et al., 'FAST-SeqS: a simple and efficient method for the detection of aneuploidy by massively parallel sequencing' PloS One, Vol.7, Issue 7, Article e41162 (internal pages 1-8) (2012) See abstract; and pages 2-5.	1-63
A	WO 2013-148496 A1 (THE JOHNS HOPKINS UNIVERSITY) 03 October 2013 See abstract; and claims 1-39.	1-63
A	WO 2013-052557 A2 (NATERA, INC.) 11 April 2013 See the whole document.	1-63
A	US 2013-0323730 A1 (AGILENT TECHNOLOGIES, INC.) 05 December 2013 See the whole document.	1-63
A	TAN et al., 'Clinical outcome of preimplantation genetic diagnosis and screening using next generation sequencing' GigaScience, Vol.3, Article 30 (internal pages 1-9) (2014) See the whole document.	1-63

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 May 2016 (02.05.2016)	**02 May 2016 (02.05.2016)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
KIM, Seung Beom
Telephone No. +82-42-481-3371

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/013346

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013-148496 A1	03/10/2013	AU 2013-240088 A1	03/10/2013
		CA 2868836 A1	03/10/2013
		CN 104350158 A	11/02/2015
		EP 2831279 A1	04/02/2015
		EP 2831279 A4	30/12/2015
		HK 1205204 A1	11/12/2015
		US 2015-0051085 A1	19/02/2015
WO 2013-052557 A2	11/04/2013	AU 2012-385961 A1	30/01/2014
		CA 2774252 A1	07/04/2011
		CA 2798758 A1	24/11/2011
		CA 2821906 A1	28/06/2012
		CA 2824387 A1	16/08/2012
		CA 2877493 A1	30/01/2014
		CN 102597266 A	18/07/2012
		CN 103608466 A	26/02/2014
		CN 103608818 A	26/02/2014
		CN 104685064 A	03/06/2015
		EP 2473638 A1	11/07/2012
		EP 2572003 A1	27/03/2013
		EP 2656263 A2	30/10/2013
		EP 2673729 A1	18/12/2013
		EP 2847347 A1	18/03/2015
		EP 2854056 A2	01/04/2015
		EP 2854056 A3	03/06/2015
		EP 2854057 A2	01/04/2015
		EP 2854057 A3	26/08/2015
		EP 2854058 A2	01/04/2015
		EP 2854058 A3	28/10/2015
		EP 2885445 A1	24/06/2015
		EP 2902500 A1	05/08/2015
		JP 2014-502845 A	06/02/2014
		JP 2014-507141 A	27/03/2014
		JP 2015-526073 A	10/09/2015
		KR 10-2015-0038216 A	08/04/2015
		US 2011-0288780 A1	24/11/2011
		US 2012-0122701 A1	17/05/2012
		US 2012-0185176 A1	19/07/2012
		US 2012-0270212 A1	25/10/2012
		US 2013-0123120 A1	16/05/2013
		US 2013-0196862 A1	01/08/2013
		US 8825412 B2	02/09/2014
		WO 2011-041485 A1	07/04/2011
		WO 2011-146632 A1	24/11/2011
		WO 2012-088456 A2	28/06/2012
		WO 2012-108920 A1	16/08/2012
		WO 2013-052557 A3	20/06/2013
		WO 2013-130848 A1	06/09/2013
		WO 2014-018080 A1	30/01/2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2016/013346

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 2014-028778 A1	20/02/2014
US 2013-0323730 A1	05/12/2013	US 9193992 B2	24/11/2015

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**02 May 2016 (02.05.2016)**
Applicant's or agent's file reference GSGE-031/01WO 29258/153	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/013346	**14 January 2016 (14.01.2016)**	15 January 2015 (15.01.2015)

International Patent Classification (IPC) or both national classification and IPC

C12Q 1/68(2006.01)i, G06F 19/22(2011.01)i

Applicant

GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea Facsimile No. +82-42-481-8578	02 May 2016 (02.05.2016)	KIM, Seung Beom Telephone No. +82-42-481-3371

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/013346

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of :

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:
      ☐ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/013346

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-63	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-63	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-63	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following documents:

D1: PloS One, Vol.7, Issue 7, Article e41162 (internal pages 1-8) (2012)
D2: WO 2013-148496 A1 (THE JOHNS HOPKINS UNIVERSITY) 03 October 2013
D3: WO 2013-052557 A2 (NATERA, INC.) 11 April 2013
D4: US 2013-0323730 A1 (AGILENT TECHNOLOGIES, INC.) 05 December 2013
D5: GigaScience, Vol.3, Article 30 (internal pages 1-9) (2014)

1. Novelty and Inventive Step

Claims 1, 18, 35, 44 and 52 relate to a method for validating a putative chromosome copy number in a genomic sample (claims 1 and 18), a method for determining a degree of relatedness between two genomic samples (claim 35), a method for detecting contamination in a sample (claim 44) and a method for determining chromosome copy number (claim 52) by using SNPs captured and sequenced by FAST-SeqS.

None of the prior art documents disclose or suggest the method comprising the SNP captured and sequenced by the FAST-SeqS. Accordingly, the subject matter of claims 1, 18, 35, 44 and 52 is neither anticipated nor rendered obvious by the prior art documents, taken alone or in combination.

Therefore, claims 1, 18, 35, 44 and 52 meet the requirements of PCT Article 33(2) and (3) with respect to novelty and inventive step.

Claims 2-17, 19-34, 36-43, 45-51 and 53-63, respectively dependent on claims 1, 18, 35, 44 and 52, also meet the requirements of PCT Article 33(2) and 33(3).

2. Industrial Applicability

Claims 1-63 are industrially applicable under PCT Article 33(4).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

ENTERED PCT DI

To:
Meyers, Thomas C.
BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference GSGE-022/01WO 208554/125	Date of mailing *(day/month/year)* 2 September 2015 (02-09-2015)
International application No. PCT/US2015/030366	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant GORE, ATHURVA	International filing date *(day/month/year)* 12 May 2015 (12-05-2015)

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46).

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   How? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 - 9.011.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with any applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

   Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

   Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer EMERY, Carole Tel: +31 (0)70 340-2848

Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
GSGE-022/01WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2015/030366	12 May 2015 (12-05-2015)	12 May 2014 (12-05-2014)
Applicant		
GORE, ATHURVA		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 3
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Petitioner Illumina, Inc., EX1003, p. 772

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/030366

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68 G06F19/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SEBASTIAN M. WASZAK ET AL: "Systematic Inference of Copy-Number Genotypes from Personal Genome Sequencing Data Reveals Extensive Olfactory Receptor Gene Content Diversity", PLOS COMPUTATIONAL BIOLOGY, vol. 6, no. 11, 11 November 2010 (2010-11-11), page e1000988, XP055160815, DOI: 10.1371/journal.pcbi.1000988 page 5 page 13, right-hand column - page 14; figure s2 ----- -/--	1-11

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 2015	02/09/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Reuter, Uwe

2

Form PCT/ISA/210 (second sheet) (April 2005)

Petitioner Illumina, Inc., EX1003, p. 773

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/030366

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/102998 A2 (HELICOS BIOSCIENCES CORP [US]; LAPIDUS STANLEY N [US]; THOMPSON JOHN F) 25 August 2011 (2011-08-25) claims 81-83; figures 7-9; example 3	1-11
X	WO 2013/177086 A1 (SEQUENOM INC [US]) 28 November 2013 (2013-11-28) pages 115,124 - page 125; claim 1 page 137	1-11
A	WO 2012/006291 A2 (LIFE TECHNOLOGIES CORP [US]; HYLAND FIONNA [US]; GOTTIMUKKALA RAJESH [] 12 January 2012 (2012-01-12) paragraph [0071] - paragraph [0079]; claims; figure 5	1-11
A	EP 2 716 766 A1 (BERRY GENOMICS CO LTD [CN]) 9 April 2014 (2014-04-09) claims	1-11

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

Petitioner Illumina, Inc., EX1003, p. 774

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/030366

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011102998 A2	25-08-2011	AU 2011218382 A1	11-10-2012
		CN 103108960 A	15-05-2013
		EP 2536852 A2	26-12-2012
		US 2010216153 A1	26-08-2010
		US 2013022977 A1	24-01-2013
		US 2014322709 A1	30-10-2014
		WO 2011102998 A2	25-08-2011
WO 2013177086 A1	28-11-2013	NONE	
WO 2012006291 A2	12-01-2012	EP 2591433 A2	15-05-2013
		US 2012046877 A1	23-02-2012
		US 2014051154 A1	20-02-2014
		WO 2012006291 A2	12-01-2012
EP 2716766 A1	09-04-2014	CN 103080336 A	01-05-2013
		EP 2716766 A1	09-04-2014
		JP 2014516541 A	17-07-2014
		US 2013130921 A1	23-05-2013
		WO 2012162884 A1	06-12-2012

Form PCT/ISA/210 (patent family annex) (April 2005)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2015/030366	12.05.2015	12.05.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C12Q1/68 G06F19/18

Applicant
GORE, ATHURVA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Reuter, Uwe Telephone No. +31 70 340-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Petitioner Illumina, Inc., EX1003, p. 777

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-11
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Petitioner Illumina, Inc., EX1003, p. 778

Re Item V

Reference is made to the following documents:

D1 Sebastian M. Waszak ET AL: "Systematic Inference of Copy-Number Genotypes from Personal Genome Sequencing Data Reveals Extensive Olfactory Receptor Gene Content Diversity", PLoS Computational Biology, vol. 6, no. 11, 11 November 2010 (2010-11-11), page e1000988, XP055160815, DOI: 10.1371/journal.pcbi.1000988

D2 WO 2011/102998 A2 (HELICOS BIOSCIENCES CORP [US]; LAPIDUS STANLEY N [US]; THOMPSON JOHN F) 25 August 2011 (2011-08-25)

D3 WO 2013/177086 A1 (SEQUENOM INC [US]) 28 November 2013 (2013-11-28)

1 **Novelty and Inventive Step** (Art. 33(2) and 33(3) PCT)

1.1 Independent claim 1 relates to a method for detecting copy number states of chromosomes in a sample based on read counts , in which a scaling factor is used to minimize the distance (see also under item VIII below) between the observed read fraction for a chromosome and the nearest whole number multiple of a control euploid read. Each chromosomal read fraction is multiplied by the scaling factor. Claim 1 does not describe how the scaling factor is derived. Claim 1 does also not describe at which stage and how a comparison between the sample chromosome(s) and the control chromosome(s) is performed.

1.2 D1 describes a method for copy numbers from sequencing reads . qPCR and microarray based experiments are performed (p.5). The calculation method comprises the use of a smoothing parameter which is used for G/C content normalization. This parameter leads to a minimization of the distance of the measurement to the nearest whole number multiple (see fig. S2, p. 13 right hand col.). Furthermore a scaling factor is used for the same purpose (p. 14) with which the read fractions are multiplied. Consequently D1 combines all technical features of claim 1.

1.3 The dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step. The technical features of said claims merely describe some of several straightforward possibilities and routine experimental optimization procedures from which the person skilled in the art would select in accordance with the circumstances, without the exercise of inventive skill, in order to solve the problem posed:

1.4 D1 focuses on the analysis of copy number states of chromosomes by analysing fragments of chromosomes. To use the elements of the method which are discussed above for the analysis of aneuploidy is however regarded as conventional for the person skilled in the art. Also the dependent claims do not seem to define how the scaling factor of claim 1 is derived and at which stage and how a comparison between the sample chromosome(s) and the control chromosome(s) is performed.

1.5 Consequently in view of D1 claim 1 lacks novelty and claims 2-11 lack inventive step.

1.6 D2 describes a method for determining chromosome copy numbers based on sequencing read counts. The read counts are adjusted to correct for a GC-bias which implicitly leads to a step of minimizing the distance of the result to the nearest whole number (example 3, fig. 7-9 ,claims 81-83). A scaling factor is not defined , but whether the correction is done by multiplication or subtraction does not seem to have a technical effect. In view of D2 the subject matter of claim 1 is not regarded as inventive. The person skilled in the art would use a scaling factor as conventional modification , when confronted with the problem of having to provide an alternative method for determining copy number. Also the dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step. The technical features of said claims merely describe some of several straightforward possibilities and routine experimental optimization procedures from which the person skilled in the art would select in accordance with the circumstances, without the exercise of inventive skill, in order to solve the problem posed.

1.7 Consequently claims 1-11 lack inventive step in view of D2.

1.8 D3 describes a method for determining copy number states by analysing the number of sequencing reads per chromosome fragment (claim 1). A scaling factor can be used to adjust the measured value to the expected value, e.g. by multiplication with a factor (p. 115) . Fetal ploidy can be analysed and different normalization and adjustment steps are described (p. 124-125). The combination of normalizing counts and adjusting the measured levels to expected levels is described (p. 137). In view of D3 the subject matter claim 1 is regarded as conventional modification of the subject matter of D3 for the person skilled in the art when confronted with the problem of having to provide an alternative method for determining copy number states. Also the dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step. The technical features of said claims merely describe some of several straightforward possibilities and routine experimental optimization procedures from which the person skilled in the art would select in accordance with the circumstances, without the exercise of inventive skill, in order to solve the problem posed.

1.9 Consequently claims 1-11 lack inventive step in view of D3.

Re item VIII

The feature of minimizing the distance between the observed fraction and a nearest whole number in claim 1 defines rather the effect which should be achieved by the use of the scaling factor , rather than technical features of the method which is used to generate a scaling factor as it is indicated in the wording of the claim. This claim wording renders the subject matter of claim 1 unclear.

Claim 1 relates to a method for detecting copy number states of chromosomes. The method however does not comprise a step of determining copy number states of chromosomes. This renders the claim unclear.

Bitte beachten Sie, dass angeführte Nichtpatentliteratur (wie z. B. wissenschaftliche oder technische Dokumente) je nach geltendem Recht dem Urheberrechtsschutz und/oder anderen Schutzarten für schriftliche Werke unterliegen könnte. Die Vervielfältigung urheberrechtlich geschützter Texte, ihre Verwendung in anderen elektronischen oder gedruckten Publikationen und ihre Weitergabe an Dritte ist ohne ausdrückliche Zustimmung des Rechtsinhabers nicht gestattet.

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XS CPRTENFRDE

BNSDOCID: <XS_____2006100103CF_I_>

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-016/01WO 29258/76	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 14/27324	International filing date *(day/month/year)* 14 March 2014 (14.03.2014)	(Earliest) Priority Date *(day/month/year)* 14 March 2013 (14.03.2013)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT PCT/US2014/027324 03.09.2014

International application No.
PCT/US 14/27324

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68, C12P 19/34 (2014.01)
USPC - 435/6.11, 435/91.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 435/6.11, 435/91.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC- C12Q1/6883, C12Q1/6837, C12Q1/6827, C12Q1/686, C12Q2525/161, C12Q2537/143, C12Q2549/113, C12Q2561/125, C12Q1/6869; C12Q2521/501; C12Q2533/107; C12Q2535/122 (2014.01); USPC- 435/6.1, 435/6.12, 435/91.2, 506/2, 506/4

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); PatBase, Google/Scholar: GOOD START GENETICS, INC.; UMBARGER, Mark; tiling, molecular inversion probes, MIP, adjacent probes, hybridize, opposite, antisense, strand, nucleic acid template, overlapping, filled-in region, Illumina, single molecule sequencing-by synthesis, universal portion, flanked

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2012/0165202 A1 (PORRECA, et al.) 28 June 2012 (28.06.2012) Abstract, claim 1; Figs 1, 11; para [0014], [0123], [0133], [0149], [0150], [0155], [0171], [0175], [0198], [0220]-[0224], [0235]-[0240], [0276], [0295], [0339]-[0354], [0376]-[0381]	1-3, 6-13 ---------- 4, 5, 14, 15
Y	THOMPSON, et al. The properties and applications of single-molecule DNA sequencing. Genome Biol. 2011, 12(2):217; Abstract, pg 3, col 2; pg 5, Fig 2 and its legend	4, 5
Y	US 2008/0269068 A1 (CHURCH, et al.) 30 October 2008 (30.10.2008) Abstract, claims 1, 6, 7; para [0081]-[0083]	14, 15

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 2014 (28.07.2014)	03 SEP 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	03 SEP 2014

Applicant's or agent's file reference	**FOR FURTHER ACTION**
GSGE-016/01WO 29258/76	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 14/27324	14 March 2014 (14.03.2014)	14 March 2013 (14.03.2013)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68, C12P 19/34 (2014.01)
USPC - 435/6.11, 435/91.1

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Fom PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	28 July 2014 (28.07.2014)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 14/27324

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 14/27324

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-15	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-15	NO
Industrial applicability (IA)	Claims	1-15	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3 and 6-13 lack an inventive step under PCT Article 33(3) as being obvious over US 2012/0165202 A1 to Porreca et al. (hereinafter "Porreca").

As to claim 1, Porreca discloses a method for analyzing a nucleic acid template, the method comprising:
obtaining a sample comprising a nucleic acid template (para [0014], "analyzing multiple genetic loci (e.g., a plurality of target nucleic acids selected from Table 1) from a patient sample, such as a blood, pre-implantation embryo, chorionic villus or amniotic fluid sample, or other sample (e.g., other biological fluid or tissue sample such as a biopsy sample)", wherein "target nucleic acid" is synonymous with "nucleic acid template");
tiling a plurality of molecular inversion probes across a portion of the template (para [0123], "FIG. 1 illustrates a non-limiting embodiment of a tiled probe layout showing ten captured sub-targets tiled across a single target. Each position in the target is covered by three sub-targets such that MIP [molecular inversion probe] performance per base pair is averaged across three probes"),
wherein immediately adjacent probes hybridize to the same strand of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner (claim 1, "each probe set comprises a plurality of different probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids flanking the same strand of one of a plurality of subregions of the target nucleic acid, wherein the subregions of the target nucleic acid are different, and wherein each subregion overlaps with at least one other subregion"; para [0123], "FIG. 1 illustrates a non-limiting embodiment of a tiled probe layout showing ten captured sub-targets tiled across a single target. Each position in the target is covered by three sub-targets such that MIP performance per base pair is averaged across three probes");
filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides (para [0339]-[0354], Example 6, "[0347] Convert Hybridized Probes into Covalently-Closed Circular Products Containing Target Nucleic Acids [0348] Prepare fill-in/ligation reaction mixture: ... [0350] 2.5 ul 10.times. Ampligase buffer (Epicentre) [0351] 5.0 ul 5 U/ul Taq Stoffel fragment (Applied Biosystems) [0352] 12.5 ul 5 U/ul Ampligase (Epicentre) [0353] 4.75 ul dH2O [0354] Add 1.0 ul of this mix to the hybridized probe reaction, and incubate at 60 C for 10 hours"); and
analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template (para [0376]-[0381], "[0376] Prepare a Shotgun Next-Generation Sequencing Library for Analysis... [0379] Mechanically shear, using either a nebulizer, BioRuptor, Hydroshear, Covaris, or similar instrument. DNA should be sheared into fragments several hundred basepairs in length. [0380] Ligate adapters required for amplification by the sequencing platform used... [0381] Perform Sequencing of Library According to Manufacturer's Directions (e.g. Illumina, ABI, etc), Reading the Target Sequence to Determine Abundance of the Target Nucleic Acid").
Porreca does not specifically disclose that immediately adjacent probes hybridize to opposite strands of the nucleic acid template. However, Porreca does disclose selecting molecular inversion probes targeting opposing strands of the DNA target (para [0171], "In some embodiments, targeting arms that can be used for capturing the repeat region of the Fragile X locus can have the following sequences or complementary to these sequences depending on the strand that is captured"). Thus, while Porreca does not specifically disclose the avoidance of probe interference by selecting alternate inversion probes so as to target opposing strands of the DNA target in alternation, it would have been obvious to one of ordinary skill in the art that genetic information is present in two equivalent complementary copies, which can be separately detected by MIP probes. It would have been further obvious to one of ordinary skill in the art that by utilizing MIPs hybridizing to both, sense and anti-sense, strands of the target nucleic acid the density of accessible for hybridization DNA target sequences would increase by up to a 100%.

As to claim 2, Porreca discloses that analyzing is by sequencing (para [0295], "Perform Sequencing of Library According to Manufacturer's Directions (e.g. Illumina, ABI, etc), Reading Both the Target Sequence and the Differentiator Tag Sequence").

As to claim 3, Porreca discloses amplifying the filled-in region of the plurality of the probes prior to sequencing (para [0276], "Amplify Circular Material by PCR Using Primers Specific to the 'Constant Region' of the Probes").

********** See Supplemental Sheet to continue **********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.: PCT/US 14/27324

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2). Citations and Explanations:

As to claims 6 and 7, Porreca discloses sequencing information comprises a mutation in the nucleic acid sequence, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), and insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof (para [0133], "Multiplex amplification strategies disclosed herein may be used analytically, as in detection of SNPs, or preparatively, often for next-generation sequencing or other sequencing techniques" para [0155], "The mutations listed in Table 2 are documented polymorphisms in several disease-associated genes... The polymorphisms are of several types: insertion/deletion polymorphisms which will cause frameshifts (and thus generally interrupt protein function) unless the insertion/deletion length is a multiple of 3 bp, and substitutions which can alter the amino acid sequence of the protein and in some cases cause complete inactivation by introduction of a stop codon").

As to claim 8, Porreca discloses that the filling-in step uses a ligase (para [0220], "Prepare fill-in/ligation reaction mixture:... [0222] 2.5 ul 10.times. Ampligase buffer (Epicentre) [0223] 5.0 ul 5 U/ul Taq Stoffel fragment (Applied Biosystems) [0224] 12.5 ul 5 U/ul Ampligase (Epicentre)").

As to claim 9, Porreca discloses that the filling-in step uses a polymerase (para [0235] "Prepare PCR mixture: ... [0240] 0.4 ul 2.5 U/ul Accuprime Pfx polymerase (Invitrogen)").

As to claim 10, Porreca discloses that a ligase is used to covalently link the filled-in region to one of the targeting arms (para [0219], "Convert Hybridized Probes into Covalently-Closed Circular Products Containing Subtargets [0220] Prepare fill-in/ligation reaction mixture:... [0222] 2.5 ul 10.times. Ampligase buffer (Epicentre)... [0224] 12.5 ul 5 U/ul Ampligase (Epicentre)").

As to claim 11, Porreca discloses that prior to sequencing, a barcode is attached to the molecular inversion probe (para [0149], "barcodes may be included, for example, to uniquely identify individual samples (e.g., patient samples) that may be mixed together"; para [0198], "In some embodiments, a sequencing technique (e.g., a next-generation sequencing technique) is used to sequence part of one or more captured targets (e.g., or amplicons thereof) and the sequences are used to count the number of different barcodes that are present. Accordingly, in some embodiments, aspects of the invention relate to a highly-multiplexed qPCR reaction", para [0175] "When a precise measurement of the length of both alleles from a diploid sample is desired, further manipulations may be required. This is because the capture efficiency measured will actually be the average efficiency of the two alleles. To effectively achieve separate measurements for each allele, barcodes (e.g., sequence tags) can be used that allow the efficiency of individual capture events (from individual genomic loci) to be followed. FIG. 11A-C shows the approach... The allele lengths can therefore be read directly off this graph, after absolute length calibration using known standards. In some embodiments, a sequencing technique (e.g., a next-generation sequencing technique) is used to sequence part of one or more captured targets (e.g., or amplicons thereof) and the sequences are used to count the number of different barcodes that are present. Accordingly, in some embodiments, aspects of the invention relate to a highly-multiplexed qPCR reaction").

As to claim 12, Porreca discloses that prior to sequencing, a sequencing adaptor is attached to the molecular inversion probe (para [0150], "The sequencing primers must be incorporated subsequently such that they sequence both the differentiator tag sequence and the target sequence. Alternatively, the sequencing adaptors can be synthesized with the random differentiator tag sequences at their 3' end (as degenerate bases), so that only one ligation must be performed. Another method is to incorporate the differentiator tag sequence into a PCR primer, such that the primer structure is arranged with the common adaptor sequence followed by the random differentiator tag sequence followed by the PCR priming sequence (in 5' to 3' order). A differentiator tag sequence and adaptor sequence (which may contain the sequencing primer site) are incorporated as tags").

As to claim 13, Porreca discloses the method according to claim 2, wherein prior to sequencing, a barcode and a sequencing adaptor are attached to the molecular inversion probe (para [0150], "The actual incorporation of the random differentiator tag sequences can be performed through various methods known in the art. For example, nucleic acids comprising differentiator tag sequences may be incorporated by ligation. This is a flexible method, because molecules having differentiator tag sequence can be ligated to any blunt-ended nucleic acids. The sequencing primers must be incorporated subsequently such that they sequence both the differentiator tag sequence and the target sequence. Alternatively, the sequencing adaptors can be synthesized with the random differentiator tag sequences at their 3' end (as degenerate bases), so that only one ligation must be performed. Another method is to incorporate the differentiator tag sequence into a PCR primer, such that the primer structure is arranged with the common adaptor sequence followed by the random differentiator tag sequence followed by the PCR priming sequence (in 5' to 3' order). A differentiator tag sequence and adaptor sequence (which may contain the sequencing primer site) are incorporated as tags").

Claims 4 and 5 lack an inventive step under PCT Article 33(3) as being obvious over Porreca, as above, in view of an article titled "The properties and applications of single-molecule DNA sequencing" by Thompson, et al. (hereinafter "Thompson").

As to claims 4 and 5, Porreca discloses analyzing of the nucleic acid template by sequencing (para [0295], "Perform Sequencing of Library According to Manufacturer's Directions (e.g. Illumina, ABI, etc), Reading Both the Target Sequence and the Differentiator Tag Sequence"), but does not specifically disclose that sequencing is done by sequencing-by-synthesis. Thompson discloses using single molecule sequencing-by-synthesis for high throughput analysis of nucleic acids (pg 5, Fig 2 and its legend, "Overview of single-molecule sequencers. The three most advanced single-molecule sequencing systems all carry out sequencing-by-synthesis using laser excitation to generate a fluorescent signal from labeled nucleotides, which is then detected using a camera") and further discloses that sequencing-by-synthesis technique is advantageous because it avoids "the many artifacts associated with reverse transcriptase and providing unparalleled quantitative accuracy" (pg 3, col 2). It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Porreca and Thompson by incorporating, in the course of routine experimentation and with a reasonable expectation of success, single molecule sequencing-by-synthesis disclosed by Thompson into the method of Porreca, to improve sensitivity and accuracy of the method of analyzing of the nucleic acid template disclosed by Porreca.

********** See the Following Supplemental Sheet to continue **********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 14/27324

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2). Citations and Explanations and the Preceding Supplemental Sheet:

Claims 14 and 15 lack an inventive step under PCT Article 33(3) as being obvious over Porreca, as above, in view of US 2008/0269068 A1 to Church, et al. (hereinafter "Church").

As to claim 14, Porreca does not specifically disclose that prior to sequencing, the molecular inversion probe is attached to a solid surface. Church, in the context of a "method of analyzing an array of nucleic acid sequences" (Church, claim 1), discloses that prior to sequencing, the molecular inversion probe is attached to a solid surface (Church, claim 1, "b) providing a plurality of molecular inversion probes, each molecular inversion probe having a tag sequence, a barcode sequence, and two guide sequences; c) hybridizing the molecular inversion probes to the immobilized query oligonucleotide sequences; d) performing rolling circle amplification such that the barcode sequence of one molecular inversion probe is transferred to one immobilized query oligonucleotide sequence; e) arraying the immobilized query oligonucleotide sequences; and f) identifying barcodes present on an immobilized query oligonucleotide sequence"; claims 6, 7, "the plurality of immobilized query oligonucleotide sequences are immobilized on beads...the beads are arranged on a solid support"). It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Porreca and Church by incorporating, in the course of routine experimentation and with a reasonable expectation of success, immobilization of the molecular inversion probe on a solid surface prior to sequencing, to facilitate analysis of the resulting sequencing reads.

As to claim 15, Porreca in view of Church discloses that the surface is a surface of a flow cell (Church, para [0081]-[0083], Example III, "[0083] 16 query adaptors will be ligated with all possible two nucleotide 3' overhangs, with 4 different 16-mer sequences associable with the identity of the 5'-most query base (magenta) (FIG. 7, Step 1). 160 different possible pairings of 40 EcoP15I and 4 query 16-mers, separated by 17-26 base pairs, should be present on every bead. Non-biotinylated strands will be denatured and washed away. The remaining strands will be immobilized and loaded into a flow cell (FIG. 7, Step 2). No further enzymology is necessary after this point. 40 four-color hybridization-imaging cycles will be performed to read four contiguous 10-mer tag sequences").

Claims 1-15 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

ENTERED IN CPI

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	13 December 2016 (13.12.2016)
Applicant's or agent's file reference GSGE-033/01WO 29258/166	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/US2016/051928**	International filing date *(day/month/year)* **15 September 2016 (15.09.2016)**
Applicant **GOOD START GENETICS, INC.**	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 . 9-011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months** from the priority date, the applicant may request that a supplementary international search be carried out by an International Searching Authority, that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/KR International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea	Authorized officer COMMISSIONER
Facsimile No. 82-42-481-8578	Telephone No. 82-42-481-5875

Form PCT/ISA/220 (July 2014)

* Attention

Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for six months(expire date : **2017.06.13**) from the date of mailing of the international search report.

http://www.kipo.go.kr/en/ => PCT Services => PCT Services

ID : PCT international application number
PW : **VAZW2H9Z**

Inquiries related to PCT International Search Report or Written Opinion prepared by KIPO as an International Searching Authority can be answered not only by KIPO but also through IPKC (Intellectual Property Korea Center), located in Vienna, VA, which functions as a PCT Help Desk for PCT applicants.

Homepage: http://www.ipkcenter.com

Email: ipkc@ipkcenter.com

Notes to Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-033/01WO 29258/166	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2016/051928**	International filing date *(day/month/year)* **15 September 2016 (15.09.2016)**	(Earliest) Priority Date *(day/month/year)* 16 September 2015 (16.09.2015)
Applicant **GOOD START GENETICS, INC.**		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 7
      ☐ as suggested by the applicant.
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/051928

A. CLASSIFICATION OF SUBJECT MATTER

G06F 19/18(2011.01)i, G06F 19/28(2011.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G06F 19/18; G06F 19/00; G06F 17/30; G06F 17/60; C12Q 1/68; G01N 33/50; G06F 19/28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: updating genomic information, clinical information, variant, evaluation, notification

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008-067551 A2 (NAVIGENICS INC.) 05 June 2008 See paragraphs [0046]-[0048], [0063]-[0065], [0105]-[0110], [0117], [0122], [0147], [0159]; claims 1, 6, 11, 20; and figure 1.	1-26
A	US 2005-0214811 A1 (MARGULIES et al.) 29 September 2005 See abstract; claim 1; and figures 1, 3.	1-26
A	US 2004-0197813 A1 (HOFFMAN et al.) 07 October 2004 See abstract; claims 1, 6, 12-13; and figure 2.	1-26
A	US 2010-0196911 A1 (HOFFMAN et al.) 05 August 2010 See abstract; claim 1; and figure 1B.	1-26
A	US 2003-0208454 A1 (REINHOFF, JR. et al.) 06 November 2003 See abstract; claim 1; and figure 4.	1-26

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 2016 (12.12.2016)	**13 December 2016 (13.12.2016)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
KIM, Seung Beom
Telephone No. +82-42-481-3371

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/051928

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008-067551 A2	05/06/2008	AU 2007-325021 A1	05/06/2008
		AU 2007-325021 B2	09/05/2013
		CA 2671267 A1	05/06/2008
		CN 101617227 A	30/12/2009
		CN 101617227 B	11/12/2013
		CN 103642902 A	19/03/2014
		CN 103642902 B	20/01/2016
		EP 2102651 A2	23/09/2009
		EP 2102651 A4	17/11/2010
		GB 2444410 A	04/06/2008
		GB 2444410 B	24/08/2011
		HK 1139737 A1	11/04/2014
		JP 2010-522537 A	08/07/2010
		JP 2014-140387 A	07/08/2014
		KR 10-2009-0105921 A	07/10/2009
		TW 200847056 A	01/12/2008
		TW I363309 B	01/05/2012
		US 2008-0131887 A1	05/06/2008
		US 2010-0293130 A1	18/11/2010
		US 9092391 B2	28/07/2015
		WO 2008-067551 A3	11/12/2008
US 2005-0214811 A1	29/09/2005	US 2005-0209787 A1	22/09/2005
		WO 2005-059692 A2	30/06/2005
		WO 2005-059692 A3	13/04/2006
US 2004-0197813 A1	07/10/2004	AU 2002-303386 B2	29/05/2008
		AU 2002-303386 B8	26/06/2008
		AU 2008-207426 A1	11/09/2008
		AU 2008-207426 B2	19/08/2010
		CA 2444717 A1	31/10/2002
		EP 1388033 A2	11/02/2004
		EP 1388033 A4	09/07/2008
		US 2002-0187483 A1	12/12/2002
		US 2004-0199333 A1	07/10/2004
		US 2005-0075794 A1	07/04/2005
		US 7983848 B2	19/07/2011
		WO 02-86663 A2	31/10/2002
		WO 02-86663 A3	22/05/2003
US 2010-0196911 A1	05/08/2010	US 2005-0074795 A1	07/04/2005
		US 7729865 B2	01/06/2010
		US 7957914 B2	07/06/2011
US 2003-0208454 A1	06/11/2003	AU 4581101 A1	24/09/2001
		AU 7521301 A1	17/12/2001
		US 2002-0019746 A1	14/02/2002
		US 2002-0133495 A1	19/09/2002
		WO 01-69430 A1	20/09/2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/051928

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 01-95059 A2	13/12/2001
		WO 01-95059 A3	28/03/2002

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTON MA 02111 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**13 December 2016 (13.12.2016)**
Applicant's or agent's file reference GSGE-033/01WO 29258/166	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/051928	**15 September 2016 (15.09.2016)**	16 September 2015 (16.09.2015)

International Patent Classification (IPC) or both national classification and IPC

G06F 19/18(2011.01)i, G06F 19/28(2011.01)i

Applicant

GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [x] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea Facsimile No. +82-42-481-8578	12 December 2016 (12.12.2016)	KIM, Seung Beom Telephone No. +82-42-481-3371

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/051928

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:
      ☐ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Petitioner Illumina, Inc., EX1003, p. 797

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/051928

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-26	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-26	NO
Industrial applicability (IA)	Claims	1-26	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following document:
D1: WO 2008-067551 A2 (NAVIGENICS INC.) 05 June 2008

1. Novelty and Inventive Step

1.1. Claims 1-15

1.1.1. Claim 1

D1, which is considered to be the closest prior art to the subject matter of claim 1, discloses a method of assessing genotype correlations of an individual, the method comprising:
obtaining a genetic sample of said individual;
generating a genomic profile for said individual;
receiving and storing the genomic profile to a computer system;
determining said individual's genotype correlations with phenotypes by comparing said individual's genomic profile to a current database of human genotype correlations with phenotypes;
updating said individual's genotype correlations by comparing said individual's genomic profile; and reporting results to said individual (see paragraph [0117]; claim 1).

Claim 1 differs from D1 in that D1 does not explicitly disclose: retrieving from a database clinical information on at least one variant in sequence data and predetermined criteria for significance.

These features, however, would be easily conceived from the feature of D1, considering that a

Continued on Supplemental Box

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2016/051928

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 2 refers to claim 2 itself, thereby rendering the definition of the subject matter of said claim unclear. Therefore, claim 2 does not meet the requirement of PCT Article 6.
(Note: The international search report and the written opinion have been established on the assumption that claim 2 refers to claim 1 instead of claim 2.)

Claims 7, 15 and 21 are unclear in that the term 'updated reported' seems to be a typographical error for 'updated report'. Therefore, claims 7, 15 and 21 do not meet the requirement of PCT Article 6
(Note: The international search report and the written opinion have been established on the assumption that the term 'updated report ed' in claims 7, 15 and 21 is regarded as 'updated report'.)

Claim 14 refers to claim 10 although it seems to rely on claim 13 for the following reason: the antecedent for the term 'the alert' in claim 14 has not been worded in claim 10, but worded in claim 13. Therefore, the matter for which protection is sought in claim 14 is not clear, contrary to PCT Article 6.
(Note: The international search report and the written opinion have been established on the assumption that claim 14 refers to claim 13.)

Claim 20 relates to a system, but said claim refers to claim 15 which relates to a method. As claim 20 does not clearly define the matter for which protection is sought, this claim does not meet the requirement of PCT Article 6.
(Note: The international search report and the written opinion have been established on the assumption that claim 20 refers to claim 16.)

Claim 26 refers to claim 26 itself, thereby rendering the definition of the subject matter of said claim unclear. Therefore, claim 26 does not meet the requirement of PCT Article 6.
(Note: The international search report and the written opinion have been established on the assumption that claim 26 refers to claim 16 instead of claim 26.)

The phrase "the method" in claim 26 has not been previously defined (PCT Article 6).

Petitioner Illumina, Inc., EX1003, p. 799

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of : Box No. V

database of human genotype correlations contains genetic variants, updates of the individual's genomic profile are made or are available in conjunction with updates to a master database as new genotype correlations emerge and are both validated and approved, and informational sources, including databases, patent publications and scientific literature, are queried for information on association of disease of condition with one or more genetic loci, wherein the informational sources are curated and assessed using quality criteria (see paragraphs [0147], [0159]; claim 20).

Accordingly, claim 1 would have been obvious over D1. Therefore, claim 1 is novel under PCT Article 33(2), but lacks an inventive step under PCT Article 33(3).

1.1.2. Claims 2-15

The additional feature of claim 2, dependent on claim 1, would be easily conceived by a person skilled in the art from the feature of D1, considering that informational sources including database are curated (see paragraph [0159]).

The additional features of claims 3-4, directly or indirectly dependent on claim 2, relating to the evaluating step comprising reading metadata entered into the database, wherein the metadata identifies at least one of a source of the update, a date of the update, and the predetermined criteria, are not explicitly disclosed in D1. However, these features are merely some of several straightforward possibilities from which a person skilled in the art would select in accordance with circumstances without the exercise of inventive skill, in order to solve the problem posed.

The additional feature of claim 5, dependent on claim 3, relating to obtaining sequence data comprising sequencing nucleic acid from the sample to obtain a plurality of sequence reads, is not explicitly disclosed in D1. However, this feature is merely one of several straightforward possibilities from which a person skilled in the art would select in accordance with circumstances without the exercise of inventive skill, in order to solve the problem posed.

The additional feature of claim 6, dependent on claim 5, would be easily conceived by a person skilled in the art from the feature of D1, considering that stored genomic profiles of a number of individuals with a specific or related phenotype may be studied to determine a

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Petitioner Illumina, Inc., EX1003, p. 800

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Previous Page

genotype common to the individuals, and a correlation may be determined (see paragraph [0107]).

The additional feature of claim 7, dependent on claim 6, would be easily conceived by a person skilled in the art from the feature of D1, considering that reports include information such as number of identical variants, links to other sites with further information on the phenotypes, and updated correlations from the latest research (see paragraphs [0046]-[0048]).

The additional feature of claim 8, dependent on claim 7, would be easily conceived by a person skilled in the art from the feature of D1, considering that if a strong correlation is found between a genetic variant and a disease for which treatment is available, detection of the genetic variant may assist in deciding to begin treatment of the disease and/or monitoring of the individual (see paragraph [0122]).

The additional feature of claim 9, dependent on claim 1, would be easily conceived by a person skilled in the art from the feature of D1, considering that the reports may also include information such as number of identical variants, and individuals have the opportunity to generate risk profile and reports with updated correlations from the latest research (see paragraphs [0046], [0048]; claim 11).

The additional feature of claim 10, dependent on claim 9, would be easily conceived by a person skilled in the art from the feature of D1, considering that scanning scientific literature for new genotype correlations may be performed periodically, for example, daily, weekly, or monthly (see paragraph [0105]; figure 1).

The additional feature of claim 11, dependent on claim 10, would be easily conceived by a person skilled in the art from the feature of D1, considering that phenotype profiles indicate a predicted prognosis, effectiveness of a treatment, or response to a treatment of a medical condition (see paragraph [0063]).

The additional feature of claim 12, dependent on claim 11, relating to at least a portion of the computer system which is provided by a cloud-based system, is not explicitly disclosed in D1. However, this feature is merely one of several straightforward possibilities from which a person skilled in the art would select in accordance with circumstances without the exercise of

Continued on The Next Page

Petitioner Illumina, Inc., EX1003, p. 801

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of : Previous Page

inventive skill, in order to solve the problem posed.

The additional feature of claim 13, dependent on claim 10, would be easily conceived by a person skilled in the art from the feature of D1, considering that the reports may be printed, saved on the subscriber's computer, or viewed on-line (see paragraph [0110]).

The additional feature of claim 14, dependent on claim 13, would be easily conceived by a person skilled in the art from the feature of D1, considering that reporting of results is through an on-line portal, wherein the on-line portal can be readily accessed by an individual through use of a computer and internet website, and telephone (see paragraph [0065]; claim 6).

The additional feature of claim 15, dependent on claim 14, would be easily conceived by a person skilled in the art from the feature of D1, considering that stored genomic profiles of a number of individuals with a specific or related phenotype may be studied to determine a genotype common to the individuals, and a correlation may be determined, and reports include information such as number of identical variants, links to other sites with further information on the phenotypes and updated correlations from the latest research (see paragraphs [0046]-[0048], [0107]).

Accordingly, claims 2-15 would have been obvious over D1. Therefore, claims 2-15 are novel under PCT Article 33(2), but lack an inventive step under PCT Article 33(3).

1.2. Claims 16-26

1.2.1. Claim 16

Claim 16 relates to a system for updating informative content of genomic information, the system comprising a processor coupled to a tangible memory subsystem storing instructions, and the features of system of claim 16 essentially correspond to those of method claim 1.

As described above in section 1.1.1, claim 1 is considered to be easily achievable from D1, and D1 further teaches a computer system to receive and store genomic profiles, analyze genotype correlations, generate rules based on the analysis of genotype correlations, apply the

Continued on The Next Page

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of : Previous Page

rules to the genomic profiles, and produce a phenotype profile and report (see paragraph [0117]).

Accordingly, claim 16 would have been obvious over D1. Therefore, claim 16 is novel under PCT Article 33(2), but lacks an inventive step under PCT Article 33(3).

1.2.2. Claims 17-26

The additional features of claims 17-26, directly or indirectly dependent on claim 16, essentially correspond to those of claims 2-4 and 6-12, respectively.

As described above in section 1.1.2, claims 2-4 and 6-12 are considered to be easily achievable from D1. Therefore, claims 17-26 are novel under PCT Article 33(2), but lack an inventive step under PCT Article 33(3).

2. Industrial Applicability

Claims 1-26 are industrially applicable under PCT Article 33(4).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

ENTERED IN CPI

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTN MA 02111 USA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference GSGE-035/01WO 29258/173	Date of mailing *(day/month/year)* 12 June 2017 (12.06.2017) **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/US2017/016498**	International filing date *(day/month/year)* **03 February 2017 (03.02.2017)**
Applicant **GOOD START GENETICS, INC.**	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:

   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 . 9-011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months** from the priority date, the applicant may request that a supplementary international search be carried out by an International Searching Authority, that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the ISA/KR International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea	Authorized officer COMMISSIONER
Facsimile No. 82-42-481-8578	Telephone No. 82-42-481-8751

Form PCT/ISA/220 (July 2014)

* Attention

Copies of the documents cited in the international search report can be searched in the following Korean Intellectual Property Office English website for six months(expire date : **2017.12.12**) from the date of mailing of the international search report.

http://www.kipo.go.kr/en/ => PCT Service => PCT Services

ID : PCT international application number
PW : **W23ABJK5**

Inquiries related to PCT International Search Report or Written Opinion prepared by KIPO as an International Searching Authority can be answered not only by KIPO but also through IPKC (Intellectual Property Korea Center), located in Vienna, VA, which functions as a PCT Help Desk for PCT applicants.

Homepage: http://www.ipkcenter.com

Email: ipkc@ipkcenter.com

Notes to Form PCT/ISA/220 (July 2014)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
MEYERS, THOMAS C.

BROWN RUDNICK LLP ONE FINANCIAL CENTER
BOSTN MA 02111 USA

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing *(day/month/year)*	**12 June 2017 (12.06.2017)**
Applicant's or agent's file reference GSGE-035/01WO 29258/173	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2017/016498	**03 February 2017 (03.02.2017)**	05 February 2016 (05.02.2016)

International Patent Classification (IPC) or both national classification and IPC
G06F 19/18(2011.01)i, G06F 19/26(2011.01)i, G06F 19/24(2011.01)i

Applicant
GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [x] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [x] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.
For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/KR	Date of completion of this opinion	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea Facsimile No. +82-42-481-8578	12 June 2017 (12.06.2017)	KIM, Seung Beom Telephone No. +82-42-481-3371

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2017/016498

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:
      ☐ in the form of an Annex C/ST.25 text file.
      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Petitioner Illumina, Inc., EX1003, p. 807

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2017/016498

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims	NONE	NO

2. Citations and explanations :

Reference is made to the following document:
D1: US 2015-0056613 A1 (SEVEN BRIDGES GENOMICS INC.) 26 February 2015

1. Novelty and Inventive Step

1.1. Claims 1-5

1.1.1. Claim 1

D1, which is considered to present the most relevant state of art, discloses methods for identifying rare variants near a structural variation in a genetic sequence, the method comprising:
aligning a Read 1 of S** to a directed acyclic graph data structure (DAG) Reference Construct 1, wherein the Read 1 of Sequence S** includes a portion of the structural variant and rare variant, and wherein the DAG represents known variants at positions within the sequence of an organism;
scoring sequence overlaps against the reference construct; and
identifying an unknown rare variant using the alignment of Read 1 to the DAG Reference Construct 1 (see abstract; paragraphs [0030], [0083], [0085]; claim 1; Figures 6A-6F)

Claim 1 differs from D1 in that D1 does not disclose: generating an in silico genome map (hereinafter 'Feature 1'); and convoluting a second path to a primary path (hereinafter 'Feature 2'). However, the Feature 1 would be easily conceived by a person skilled in the art from the feature of D1, considering that the DAG is represented in computer memory, and an algorithm is used to align sequence reads against the DAG (see paragraphs [0054], [0057]). And the Feature 2 is merely one of several straightforward possibilities from which the skilled person

Continued on Supplemental Box

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2017/016498

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The word "computer" in claims 5-6, has not been previously defined. Therefore, claims 5-6 are not clear and are contrary to the requirement of PCT Article 6.

The phrase "path;." in claim 8 is considered to be a typographical error for 'path.'(PCT Article 6).

Petitioner Illumina, Inc., EX1003, p. 809

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box No. V

would select in accordance with circumstances without the exercise of inventive skill, considering that the alignment of Read 1 to the DAG Reference Construct 1 allows one to identify the unknown rare variant not as a sequencing error by virtue of being a part of an otherwise well-aligned and high scoring read in D1 (see paragraph [0085]).

Accordingly, claim 1 would have been obvious over D1. Therefore, claim 1 lacks an inventive step under PCT Article 33(3).

1.1.2. Claims 2-5

The additional feature of claim 2 dependent on claim 1 would be easily conceived by a person skilled in the art from the feature of D1 considering that an alignment of a known rare variant near a known structural variant using DAG reference constructs of the invention, and the goal of sequence alignment is to combine the set of nucleic acid reads produced by the sequencer to achieve a longer read (see paragraphs [0004], [0086]; figures 6E-6F).

The additional features of claims 3-4 directly or indirectly dependent on claim 2 are merely some of several straightforward possibilities from which the skilled person would select in accordance with circumstances without the exercise of inventive skill, considering that the alignment of a known rare variant near a known structural variant using DAG reference constructs of the invention, and the goal of sequence alignment to combine the set of nucleic acid reads produced by the sequencer to achieve a longer read in D1 (see paragraphs [0004], [0086]; figures 6E-6F).

The additional feature of claim 5 dependent on claim 1 would be easily conceived by a person skilled in the art from the feature of D1 considering that the DAG is represented in computer memory, and each variant in the DAG is tagged with correlated diagnostic information (see paragraphs [0030], [0054]).

Accordingly, claims 2-5 would have been obvious over D1. Therefore, claims 2-5 lack an inventive step under PCT Article 33(3).

1.2. Claims 6-9

Continued on The Next Page

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Previous Page

1.2.1. Claim 6

D1 discloses methods for identifying rare variants near a structural variation in a genetic sequence, the method comprising:
aligning a Read 1 of S** to a directed acyclic graph data structure (DAG) Reference Construct 1, wherein the Read 1 of Sequence S** includes a portion of the structural variant and rare variant, and wherein the DAG represents known variants at positions within the sequence of an organism in computer memory;
scoring sequence overlaps against the reference construct; and
identifying an unknown rare variant using the alignment of Read 1 to the DAG Reference Construct 1 (see abstract; paragraphs [0030], [0054], [0083], [0085]; claim 1; Fig. 6A-6F).

Claim 6 differs from D1 in that D1 does not disclose: generating an in silico genome map (hereinafter 'Feature 1'); and a plurality of sequence reads generated by sequencing nucleic acid from a sample (hereinafter 'Feature 2'). However, the Feature 1 would be easily conceived by a person skilled in the art from the feature of D1, considering that the DAG is represented in the computer memory, and an algorithm is used to align sequence reads against the DAG (see paragraphs [0054], [0057]). And the Feature 2 would be easily conceived by a person skilled in the art from the feature of D1, considering that the DAG has been created against which nucleic acid reads can be aligned, and the nucleic acid can be extracted from a biological sample (see paragraphs [0052], [0133]).

Accordingly, claim 6 would have been obvious over D1. Therefore, claim 6 lacks an inventive step under PCT Article 33(3).

1.2.2. Claims 7-9

The additional features of claims 7-9 directly or indirectly dependent on claim 6 would be easily conceived by a person skilled in the art from the feature of D1 considering aligning a Read 1 of S** to the directed acyclic graph data structure (DAG) Reference Construct 1; scoring sequence overlaps against the reference construct; and identifying the unknown rare variant using the alignment of Read 1 to the DAG Reference Construct 1, wherein the alignment of Read 1 to the DAG Reference Construct 1 allows one to identify the unknown rare variant not as a sequencing error by virtue of being a part of an otherwise well-aligned

Continued on The Next Page

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of : Previous Page

and high scoring read (see paragraph [0085]; claim 1).

Accordingly, claims 7-9 would have been obvious over D1. Therefore, claims 7-9 lack an inventive step under PCT Article 33(3).

2. Industrial Applicability

Claims 1-9 are industrially applicable under PCT Article 33(4).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-035/01WO 29258/173	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. **PCT/US2017/016498**	International filing date *(day/month/year)* **03 February 2017 (03.02.2017)**	(Earliest) Priority Date *(day/month/year)* 05 February 2016 (05.02.2016)
Applicant **GOOD START GENETICS, INC.**		

This International search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of :
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☐ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. With regard to the drawings,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 2
      ☐ as suggested by the applicant.
      ☒ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/016498

A. CLASSIFICATION OF SUBJECT MATTER

G06F 19/18(2011.01)i, G06F 19/26(2011.01)i, G06F 19/24(2011.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G06F 19/18; G06F 19/22; C12Q 1/68; C40B 30/04; G06F 19/26; G06F 19/24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: variant detection, rare variant, in silico genome map, aligning, convoluting

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015-0056613 A1 (SEVEN BRIDGES GENOMICS INC.) 26 February 2015 See abstract; paragraphs [0004], [0030], [0052], [0054], [0057], [0083]-[0086], [0133]; claim 1; and figures 6A-6F.	1-9
A	US 2014-0129201 A1 (GOOD START GENETICS, INC.) 08 May 2014 See claims 1-11; and figure 7.	1-9
A	WO 2015-089333 A1 (ACCURAGEN, INC.) 18 June 2015 See claims 1-2.	1-9
A	US 2016-0034638 A1 (UNIVERSITY OF ROCHESTER) 04 February 2016 See claim 1; and figures 1-2.	1-9
A	US 2015-0178445 A1 (THE BROAD INSTITUTE, INC.) 25 June 2015 See claim 1; and figure 5.	1-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2017 (12.06.2017)	**12 June 2017 (12.06.2017)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea
Facsimile No. +82-42-481-8578

Authorized officer
KIM, Seung Beom
Telephone No. +82-42-481-3371

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2017/016498

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015-0056613 A1	26/02/2015	AU 2014-308794 A1	10/03/2016
		AU 2014-324438 A1	14/04/2016
		CA 2921645 A1	26/02/2015
		CA 2925335 A1	02/04/2015
		CN 105637098 A	01/06/2016
		CN 105793859 A	20/07/2016
		EP 3036344 A1	29/06/2016
		EP 3053073 A1	10/08/2016
		JP 2016-536698 A	24/11/2016
		JP 2016-540275 A	22/12/2016
		KR 10-2016-0047506 A	02/05/2016
		KR 10-2016-0062127 A	01/06/2016
		US 2015-0057946 A1	26/02/2015
		US 2015-0347678 A1	03/12/2015
		US 2016-0306921 A1	20/10/2016
		US 9116866 B2	25/08/2015
		US 9390226 B2	12/07/2016
		WO 2015-027050 A1	26/02/2015
		WO 2015-048753 A1	02/04/2015
US 2014-0129201 A1	08/05/2014	CA 2888779 A1	15/05/2014
		EP 2917881 A1	16/09/2015
		EP 2917881 A4	20/07/2016
		WO 2014-074246 A1	15/05/2014
WO 2015-089333 A1	18/06/2015	AU 2014-362227 A1	23/06/2016
		CA 2933343 A1	18/06/2015
		CN 104946737 A	30/09/2015
		EP 3080298 A1	19/10/2016
		HK 1214843 A1	05/08/2016
		KR 10-2016-0106596 A	12/09/2016
		SG 11201604737V A	28/07/2016
		US 2016-0304954 A1	20/10/2016
US 2016-0034638 A1	04/02/2016	WO 2014-152990 A1	25/09/2014
US 2015-0178445 A1	25/06/2015	EP 2891099 A1	08/07/2015
		EP 2891099 A4	20/04/2016
		WO 2014-036167 A1	06/03/2014

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing *(day/month/year)*	25 FEB 2013
Applicant's or agent's file reference GSGE-008/01WO 29258/45	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 12/55362	International filing date *(day/month/year)* 14 September 2012 (14.09.2012)
Applicant GOOD START GENETICS, INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GSGE-008/01WO 29258/45	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 12/55362	International filing date *(day/month/year)* 14 September 2012 (14.09.2012)	(Earliest) Priority Date *(day/month/year)* 17 October 2011 (17.10.2011)
Applicant GOOD START GENETICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established by this Authority to read as follows:

Methods of identifying mutations associated with diseases

5. With regard to the **abstract**,
   ☐ the text is approved as submitted by the applicant.
   ☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☒ none of the figures is to be published with the abstract.

Form PCT/ISA/210 (first sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55362

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-20, drawn to a method for identifying a novel mutation associated with a disease, the method comprising: obtaining nucleic acid from a subject having a disease; identifying at least one mutation in the nucleic acid; and comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations, as indicated in claims 1 or 11; or a method for determining if a mutation is causative of a disease, as indicated in claim 20. The first named invention (claims 1-5, 7-8, 11-14, 16-17) is limited to wherein identifying comprising: sequencing the nucleic acid; wherein sequencing is sequencing-by-synthesis, and wherein the disease is cystic fibrosis. **********Continued in the extra sheet****

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5, 7-8, 11-14, 16-17, limited to wherein identifying comprising: sequencing the nucleic acid; wherein sequencing is sequencing-by-synthesis, and wherein the disease is cystic fibrosis

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55362

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The disclosure relates to methods for analyzing nucleic acids to identify mutations associated with diseases. More specifically, the methods of the invention involve obtaining nucleic acid from a subject having a disease, identifying at least one mutation in the nucleic acid, and comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as newly identified mutations.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55362

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2013.01)
USPC - 435/6.11, 435/6.12, 435/6.17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C12Q 1/68 (2013.01)
USPC - 435/6.11, 435/6.12, 435/6.17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - C12Q 1/68 (2013.01) - see keyword below
USPC - 435/6.11, 435/6.12, 435/6.17 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); PatBase; Medline, Google: sequencing-by-synthesis, SBS, identifying, determine, screen, novel, mutation, new, disorder, disease, cancer, cystic fibrosis, mutation database, compare, sequencing-by-synthesis, single-molecule, obtain, sample, control, normal, Hispanic, nucleic acid, nucleotide, polynucleotide, DNA, RNA,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	CASTELLANI et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros. 2008, Vol. 7(3), p. 179-96. Abstract; pg 180, col 1, and col 2, lower para; pg 181, col 2, para 2; pg 182, col 2, para 1 and 3, and Table 2; pg 183, col 1, para 2, and col 2, para 1 and 2, and last para; pg 185, col 1, last para, and col 2, para 1; pg 186, col 1, para 3; pg 187, Table 5; pg 191, Table 7 and Table 8; pg 192, col 1, last para; and pg 193, col 1, Ref 4	1-2, 5, 7-8, 11,14, 16-17 --- 3-4, 12-13
Y	US 2011/0166029 A1 (MARGULIES et al.) 07 July 2011 (07.07.2011), para [0044], [0048], [0057], [0059], and [0064]	3-4, 12-13
A	SCHADT et al. A window into third-generation sequencing. Hum Mol Genet. 2010, Vol. 19(R2), p. R227-40. Epub 2010 Sep 21. pg R227, col 1, and col 2, middle para; pg R230, Table 1; and pg R231, col 1, last para	1-5, 7-8, 11-14, 16-17
A	NAN et al. A novel CFTR mutation found in a Chinese patient with cystic fibrosis. Comparing with normal database. Chinese Med J. 2006, Vol. 119(2), p. 103-109. Entire documentation, especially Abstract	1-5, 7-8, 11-14, 16-17
A	CHOE et al. Novel CFTR Mutations in a Korean Infant with Cystic Fibrosis and Pancreatic Insufficiency. J Korean Med Sci. 2010; Vol. 25, p. 163-5. Entire documentation, especially Abstract	1-5, 7-8, 11-14, 16-17
A	US 2011/0230365 A1 (ROHLFS et al.) 22 September 2011 (22.09.2011), Abstract, para [0005], [0071], [011], [0138], and [0150]	1-5, 7-8, 11-14, 16-17

☒ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 February 2013 (07.02.2013)	25 FEB 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55362

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0192047 A1 (PARR et al.) 30 July 2009 (30.07.2009), para [0010], [0030], [0045], [0158], and [0200]	1-5, 7-8, 11-14, 16-17

Form PCT/ISA/210 (continuation of second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/55362

Continuation of:
Box No III (unity of invention is lacking)

(Continuation of Group I+) Applicant is invited to elect an additional features, selected from: 1) wherein prior to identifying, the method further comprises attaching a barcode sequence to the nucleic acid (claims 6 and 15); or/and 2) the method further comprising determining of the novel mutation is causative of the disease, or a method for determining if a mutation is causative of a disease, comprising: identifying at least one novel mutation in the sequence, annotating the mutation with appropriate functional information, as indicated in claim 20 (claims 9-10, 18-19, 20), to be searched by paying additional fee for each election. Further provided are exemplary elections: 1) if the an additional feature wherein the method further comprises attaching a barcode sequence to the nucleic acid (claims 6 and 15) is elected, claims 6 and 15 will be searched by paying an additional fee; 2) if the additional feature of the method further comprising determining of the novel mutation is causative of the disease, or a method for determining if a mutation is causative of a disease comprising identifying at least one novel mutation in the sequence, annotating the mutation with appropriate functional information (claims 9-10, 18-19, 20) is elected, claims 9-10, 18-20 will be searched by paying an additional fee; and 3) both additional features 1) and 2) are elected, all additional claims 6, 9-10, 15, and 18-20 will be searched by paying 2X additional fees.

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Among Group I+, claims 1-8 and 11-17 do not include the inventive concept of determining of the novel mutation is causative of the disease as required by the claims, annotating the mutation with appropriate functional information, as required by claims 9-10 and 18-20; and claims 1-5, 7-14, and 16-20 do not include the inventive concept of attaching a barcode sequence to the nucleic acid, as required by claims 6 and 15.

The inventions of Groups I+ share the technical feature of determining if a mutation associated with a disease, comprising: obtaining a nucleic acid sequence from a subject having a disease, identifying at least one mutation in the nucleic acid; and claims 1-19 of Group I+ further share the technical feature of identifying a novel mutation associated with a disease, the method comprising: obtaining nucleic acid from a subject having a disease; identifying at least one mutation in the nucleic acid; and comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations. However, this shared technical feature does not represent a contribution over prior art as being obvious over an article entitled 'Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice' by CASTELLANI et al. (hereinafter 'Castellani'; J Cyst Fibros. 2008, Vol. 7(3), p. 179-96) as follows:Castellani discloses a method for identifying a novel mutation associated with a disease (pg 183, col 1, para 2 ? 'Conclusion:...methods to detect mutations in the CFTR gene ... to extensive scanning/sequencing protocols that enable the detection of novel mutations', wherein 'novel mutations' 'in the CFTR gene' is 'associated with a disease' - 'cystic fibrosis (CF)'; pg 180, col 1 - 'cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene ... have resulted in the identification of more than 1500 CFTR mutations'; Abstract),
--- the method comprising: obtaining nucleic acid from a subject having a disease (pg 182, col 2, para 1 - 'identification of CFTR mutations in patients diagnosed with CF'; pg 180, col 1 - 'cystic fibrosis (CF)'; pg 191, Table 7 - 'Name of patient ... sample number'; pg 191, Table 8 - 'Molecular genetic analysis for cystic fibrosis....Sample type: DNA')
---identifying at least one mutation in the nucleic acid (pg 183, col 2, para 2 - 'diagnosis of CF is based on a consistent phenotype plus evidence of CFTR channel dysfunction ... or identification of two CF-disease causing mutation in trans'; pg 183, col 2, last para - 'the term "mutation" is defined as a molecular alteration in the DNA sequence of a gene; pg 182, col 2, para 1 - 'identification of CFTR mutations in patients diagnosed with CF').
Although Castellani does not expressively teach comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations, one of ordinary skill in the art at the time the invention was made would have known to do so, because it is the first step that one would have done to compare the mutation to a database of mutations in order to classify the mutation or to determine if the mutation identified is a novel mutation, especially Castellani further provides a database of mutations known to be associated with the disease, which is widely used by researchers in the field (pg 192, col 1, last para - 'The traditional mutation nomenclature is currently used in the vast majority of research papers, and in the CFGAC Mutation Database...we advise using the mutation names of the routinely and widely used CFTR mutation database [4]', wherein 'CFGAC Mutation Database' is 'a database of mutations known to be associated with the disease' - 'cystic fibrosis (CF)'; pg 181, col 2, para 2 - 'more than 1500 sequence alterations have been identified in the CFTR gene and their listing is continuously updated within the Cystic Fibrosis Genetic Analysis Consortium (CFGAC) database [4]'; pg 193, col 1, References - '[4] Cystic Fibrosis Mutation Database. www.genet.sickkids.on.ca/cftr'); the classification of the mutations (pg 187, Table 5), as well as teaches criteria for characterization of novel mutations for determining the potential pathogenic potential of the mutation identified (pg 185, col 1, last para - 'Other criteria can be used to asses the pathogenic potential,..include: - the sequence variation causes a novel amino acid sequence ...the sequence variant changes a highly evolutionarily conserved amino acid residue...the sequence variation creates a novel/cryptic splice site...similar sequence variations are found in other ABC genes'). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to compare the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS C. MEYERS
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* 25 FEB 2013
Applicant's or agent's file reference GSGE-008/01WO 29258/45	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 12/55362	14 September 2012 (14.09.2012)	17 October 2011 (17.10.2011)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68 (2013.01)
USPC - 435/6.11, 435/6.12, 435/6.17

Applicant GOOD START GENETICS, INC.

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [X] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	07 February 2013 (07.02.2013)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/55362

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/55362

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicahle, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+, claims 1-20, drawn to a method for identifying a novel mutation associated with a disease, the method comprising: obtaining nucleic acid from a subject having a disease; identifying at least one mutation in the nucleic acid; and comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations, as indicated in claims 1 or 11; or a method for determining if a mutation is causative of a disease, as indicated in claim 20. The first named invention (claims 1-5, 7-8, 11-14, 16-17) is limited to wherein identifying comprising: sequencing the nucleic acid; wherein sequencing is sequencing-by-synthesis, and wherein the disease is cystic fibrosis. Applicant is invited to elect an additional features, selected from: 1) wherein prior to identifying, the method further comprises attaching a barcode sequence to the nucleic acid (claims 6 and 15); or/and 2) the method further comprising determining of the novel mutation is causative of the disease, or a method for determining if a mutation is causative of a disease, comprising: identifying at least one novel mutation in the sequence, annotating the mutation with appropriate functional information, as indicated in claim 20 (claims 9-10, 18-19, 20), to be searched by paying additional fee for each election. Further provided are exemplary elections: 1) if the an additional feature wherein the method further comprises attaching a barcode sequence to the nucleic acid (claims 6 and 15) is elected, claims 6 and 15 will be searched by paying an additional fee; 2) if the additional feature of the method further comprising determining of the novel mutation is causative of the disease, or a method for determining if a mutation is causative of a disease comprising identifying at least one novel mutation in the sequence, annotating the mutation with appropriate functional information (claims 9-10, 18-19, 20) is elected, claims 9-10, 18-20 will be searched by paying an additional fee; and 3) both additional features 1) and 2) are elected, all additional claims 6, 9-10, 15, and 18-20 will be searched by paying 2X additional fees.

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Among Group I+, claims 1-8 and 11-17 do not include the inventive concept of determining of the novel mutation is causative of the disease as required by the claims, annotating the mutation with appropriate functional information, as required by claims 9-10 and 18-20; and claims 1-5, 7-14, and 16-20 do not include the inventive concept of attaching a barcode sequence to the nucleic acid, as required by claims 6 and 15.

The inventions of Groups I+ share the technical feature of determining if a mutation associated with a disease, comprising: obtaining a nucleic acid sequence from a subject having a disease, identifying at least one mutation in the nucleic acid; and claims 1-19 of Group I+ further share the technical feature of identifying a novel mutation associated with a disease, the method comprising: obtaining nucleic acid from a subject having a disease; identifying at least one mutation in the nucleic acid; and comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations. However, this shared technical feature does not represent a contribution over prior art as being obvious over an article entitled 'Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice' by CASTELLANI et al. (hereinafter 'Castellani'; J Cyst Fibros. 2008, Vol. 7(3), p. 179-96) as follows:

**********Continued in the supplemental box**********

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-5, 7-8, 11-14, 16-17, see above for limitations

Form PCT/ISA/237 (Box No. IV) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/55362

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-5, 7-8, 11-14, 16-17	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-5, 7-8, 11-14, 16-17	NO
Industrial applicability (IA)	Claims	1-5, 7-8, 11-14, 16-17	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-2, 5, 7-8, 11, 14, and 16-17 lack an inventive step under PCT Article 33(3) as being obvious over an article entitled 'Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice' by CASTELLANI et al. (hereinafter 'Castellani').

Regarding claim 1, Castellani discloses a method for identifying a novel mutation associated with a disease (pg 183, col 1, para 2 - 'Conclusion:...methods to detect mutations in the CFTR gene ... to extensive scanning/sequencing protocols that enable the detection of novel mutations', wherein 'novel mutations' 'in the CFTR gene' is 'a novel mutation associated with a disease' - 'cystic fibrosis (CF)'; pg 180, col 1 - 'cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene ... have resulted in the identification of more than 1500 CFTR mutations'; Abstract),
--- the method comprising: obtaining nucleic acid from a subject having a disease (pg 182, col 2, para 1 - 'identification of CFTR mutations in patients diagnosed with CF'; pg 180, col 1 - 'cystic fibrosis (CF)'; pg 191, Table 7 - 'Name of patient ... sample number'; pg 191, Table 8 - 'Molecular genetic analysis for cystic fibrosis....Sample type: DNA');
---identifying at least one mutation in the nucleic acid (pg 183, col 2, para 2 - 'diagnosis of CF is based on a consistent phenotype plus evidence of CFTR channel dysfunction ... or identification of two CF-disease causing mutation in trans'; pg 183, col 2, last para - 'the term "mutation" is defined as a molecular alteration in the DNA sequence of a gene; pg 182, col 2, para 1 - 'identification of CFTR mutations in patients diagnosed with CF').

Although Castellani does not expressively teach comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations, one of ordinary skill in the art at the time the invention was made would have known to do so, because it is the first step that one of the ordinary skill in the art would have done to compare the mutation to a database of mutations in order to classify the mutation or to determine if the mutation identified is a novel mutation, especially Castellani further provides a database of mutations known to be associated with the disease, which is widely used by researchers in the field (pg 192, col 1, last para - 'The traditional mutation nomenclature is currently used in the vast majority of research papers, and in the CFGAC Mutation Database...we advise using the mutation names of the routinely and widely used CFTR mutation database [4]', wherein 'CFGAC Mutation Database' is 'a database of mutations known to be associated with the disease' - 'cystic fibrosis (CF)'; pg 181, col 2, para 2 - 'more than 1500 sequence alterations have been identified in the CFTR gene and their listing is continuously updated within the Cystic Fibrosis Genetic Analysis Consortium (CFGAC) database [4]'; pg 193, col 1, References - '[4] Cystic Fibrosis Mutation Database. www.genet.sickkids.on.ca/cftr'); the classification of the mutations (pg 187, Table 5), as well as teaches criteria for characterization of novel mutations for determining the potential pathogenic potential of the mutation identified (pg 185, col 1, last para - 'Other criteria can be used to asses the pathogenic potential,..include: - the sequence variation causes a novel amino acid sequence ...the sequence variant changes a highly evolutionarily conserved amino acid residue...the sequence variation creates a novel/cryptic splice site...similar sequence variations are found in other ABC genes'). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to identify a novel mutation by comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations.

Regarding claim 2, Castellani obviates the method according to claim 1, and Castellani further discloses wherein identifying comprising: sequencing the nucleic acid (pg 182, col 2, para 3 - 'Sequencing is then used to characterize the abnormal pattern....although it has become feasible to sequence the entire CFTR gene in the diagnostic setting...Sequencing is also used when the mutation under investigation cannot be detected by alternative direct techniques'; pg 183, col 1, para 2 - 'Conclusion: Current analytic methods to detect mutations in the CFTR gene ... to extensive scanning/sequencing protocols that enable the detection of novel mutations'); and
---comparing the sequence of the nucleic acid from the sample to a reference sequence (pg 185, col 1, last para - 'the sequence variation causes a novel amino acid sequence that does not occur in the normal CFTR gene from at least 100 carriers of CF mutations from the patients ethnic group', which can only be obtained by 'comparing the sequence of the nucleic acid from the sample to a reference sequence').

**********Continued in the supplemental box**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/55362

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No IV (Lack of unity of invention)

Castellani discloses a method for identifying a novel mutation associated with a disease (pg 183, col 1, para 2 . 'Conclusion:...methods to detect mutations in the CFTR gene ... to extensive scanning/sequencing protocols that enable the detection of novel mutations', wherein 'novel mutations' 'in the CFTR gene' is 'associated with a disease' - 'cystic fibrosis (CF)'; pg 180, col 1 - 'cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene ... have resulted in the identification of more than 1500 CFTR mutations'; Abstract), --- the method comprising: obtaining nucleic acid from a subject having a disease (pg 182, col 2, para 1 - 'identification of CFTR mutations in patients diagnosed with CF'; pg 180, col 1 - 'cystic fibrosis (CF)'; pg 191, Table 7 - 'Name of patient ... sample number'; pg 191, Table 8 - 'Molecular genetic analysis for cystic fibrosis....Sample type: DNA')
---identifying at least one mutation in the nucleic acid (pg 183, col 2, para 2 - 'diagnosis of CF is based on a consistent phenotype plus evidence of CFTR channel dysfunction ... or identification of two CF-disease causing mutation in trans'; pg 183, col 2, last para - 'the term "mutation" is defined as a molecular alteration in the DNA sequence of a gene; pg 182, col 2, para 1 - 'identification of CFTR mutations in patients diagnosed with CF').

Although Castellani does not expressively teach comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations, one of ordinary skill in the art at the time the invention was made would have known to do so, because it is the first step that one would have done to compare the mutation to a database of mutations in order to classify the mutation or to determine if the mutation identified is a novel mutation, especially Castellani further provides a database of mutations known to be associated with the disease, which is widely used by researchers in the field (pg 192, col 1, last para - 'The traditional mutation nomenclature is currently used in the vast majority of research papers, and in the CFGAC Mutation Database...we advise using the mutation names of the routinely and widely used CFTR mutation database [4]', wherein 'CFGAC Mutation Database' is 'a database of mutations known to be associated with the disease' - 'cystic fibrosis (CF)'; pg 181, col 2, para 2 - 'more than 1500 sequence alterations have been identified in the CFTR gene and their listing is continuously updated within the Cystic Fibrosis Genetic Analysis Consortium (CFGAC) database [4]'; pg 193, col 1, References - '[4] Cystic Fibrosis Mutation Database. www.genet.sickkids.on.ca/cftr'); the classification of the mutations (pg 187, Table 5), as well as teaches criteria for characterization of novel mutations for determining the potential pathogenic potential of the mutation identified (pg 185, col 1, last para - 'Other criteria can be used to asses the pathogenic potential,..include: - the sequence variation causes a novel amino acid sequence ...the sequence variant changes a highly evolutionarily conserved amino acid residue...the sequence variation creates a novel/cryptic splice site...similar sequence variations are found in other ABC genes'). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to compare the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/55362

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V No 2 (citations and explanations)

Regarding claim 5, Castellani further obviates the method according to claim 2, wherein the reference sequence is a consensus human sequence (pg 185, col 2, para 1 - 'Indirect evidence that a CFTR sequence variations does not cause CF is:... an intronic sequence variation outside the known consensus sites and which does not create a splicing site', wherein 'the known consensus sites' indicating ' wherein the reference sequence is a consensus human sequence', furthermore, it is a common practice to use 'a consensus human sequence' as a 'reference sequence' for human gene comparison; pg 180, col 1 - 'cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene ... have resulted in the identification of more than 1500 CFTR mutations'; pg 180, col 2, lower para - 'Cystic Fibrosis Society ..Human Genetics')
--- or a sequence from a non-diseased sample (pg 186, col 1, para 3 - 'If a missense mutation which involved a highly evolutionarily conserved amino acid, and which was not found in a set of control individuals, was identified in a CF patient, it was defined as a Cf causing mutation', wherein ' a set of control individuals' indicating 'a sequence from a non-diseased sample'; pg 180, col 1 - 'cystic fibrosis (CF)').

Regarding claim 7, Castellani obviates the method according to claim 1, and Castellani further discloses wherein the disease is cystic fibrosis (pg 183, col 1, para 2 - 'Conclusion: Current analytic methods to detect mutations in the CFTR gene ... to extensive scanning/sequencing protocols that enable the detection of novel mutations', wherein 'novel mutations' 'in the CFTR gene' is 'associated with a disease' - 'cystic fibrosis (CF)'; pg 180, col 1 - 'cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene ... have resulted in the identification of more than 1500 CFTR mutations'; Abstract).

Regarding claim 8, Castellani obviates the method according to claim 7, and Castellani further discloses wherein the subject is the subject is Hispanic (pg 182, Table 2 - 'CFTR mutations in selected populations' - col 2 in Table 2, section 3 - 'Hispanic').

Regarding claim 11, Castellani discloses a method for identifying a novel mutation associated with a disease (pg 183, col 1, para 2 - 'Conclusion:...methods to detect mutations in the CFTR gene ... to extensive scanning/sequencing protocols that enable the detection of novel mutations', wherein 'novel mutations' 'in the CFTR gene' is 'a novel mutation associated with a disease' - 'cystic fibrosis (CF)'; pg 180, col 1 - 'cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene ... have resulted in the identification of more than 1500 CFTR mutations'; Abstract), the method comprising:
---obtaining nucleic acid from a subject having a disease (pg 182, col 2, para 1 - 'identification of CFTR mutations in patients diagnosed with CF'; pg 180, col 1 - 'cystic fibrosis (CF)'; pg 191, Table 7 - 'Name of patient ... sample number'; pg 191, Table 8 - 'Molecular genetic analysis for cystic fibrosis....Sample type: DNA');
---sequencing the nucleic acid (pg 182, col 2, para 3 - 'Sequencing is then used to characterize the abnormal pattern....although it has become feasible to sequence the entire CFTR gene in the diagnostic setting...Sequencing is also used when the mutation under investigation cannot be detected by alternative direct techniques'; pg 183, col 1, para 2 - 'Conclusion: Current analytic methods to detect mutations in the CFTR gene ... to extensive scanning/sequencing protocols that enable the detection of novel mutations');
---comparing the sequence of the nucleic acid from the sample to a reference sequence, thereby identifying mutations in the nucleic acid (pg 185, col 1, last para - 'the sequence variation causes a novel amino acid sequence that does not occur in the normal CFTR gene from at least 100 carriers of CF mutations from the patients ethnic group', which can only be obtained by 'comparing the sequence of the nucleic acid from the sample to a reference sequence, thereby identifying mutations in the nucleic acid').
Although Castellani does not expressively teach comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations, one of ordinary skill in the art at the time the invention was made would have known to do so, because it is the first step that one of the ordinary skill in the art would have done to compare the mutation to a database of mutations in order to classify the mutation or to determine if the mutation identified is a novel mutation, especially Castellani further provides a database of mutations known to be associated with the disease, which is widely used by researchers in the field (pg 192, col 1, last para - 'The traditional mutation nomenclature is currently used in the vast majority of research papers, and in the CFGAC Mutation Database...we advise using the mutation names of the routinely and widely used CFTR mutation database [4]', wherein 'CFGAC Mutation Database' is 'a database of mutations known to be associated with the disease' - 'cystic fibrosis (CF)'; pg 181, col 2, para 2 - 'more than 1500 sequence alterations have been identified in the CFTR gene and their listing is continuously updated within the Cystic Fibrosis Genetic Analysis Consortium (CFGAC) database [4]'; pg 193, col 1, References - '[4] Cystic Fibrosis Mutation Database. www.genet.sickkids.on.ca/cftr'); the classification of the mutations (pg 187, Table 5), as well as teaches criteria for characterization of novel mutations for determining the potential pathogenic potential of the mutation identified (pg 185, col 1, last para - 'Other criteria can be used to asses the pathogenic potential,..include: - the sequence variation causes a novel amino acid sequence ...the sequence variant changes a highly evolutionarily conserved amino acid residue...the sequence variation creates a novel/cryptic splice site...similar sequence variations are found in other ABC genes'). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to identify a novel mutation by comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations.

Regarding claim 14, Castellani further obviates the method according to claim 11, wherein the reference sequence is a consensus human sequence (pg 185, col 2, para 1 - 'Indirect evidence that a CFTR sequence variations does not cause CF is:... an intronic sequence variation outside the known consensus sites and which does not create a splicing site', wherein 'the known consensus sites' indicating ' wherein the reference sequence is a consensus human sequence', furthermore, it is a common practice to use 'a consensus human sequence' as a 'reference sequence' for human gene comparison; pg 180, col 1 - 'cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene ... have resulted in the identification of more than 1500 CFTR mutations'; pg 180, col 2, lower para - 'Cystic Fibrosis Society ..Human Genetics')
---or a sequence from a non-diseased sample (pg 186, col 1, para 3 - 'If a missense mutation which involved a highly evolutionarily conserved amino acid, and which was not found in a set of control individuals, was identified in a CF patient, it was defined as a Cf causing mutation', wherein ' a set of control individuals' indicating 'a sequence from a non-diseased sample'; pg 180, col 1 - 'cystic fibrosis (CF)').

**********Continued in the next supplemental box**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/55362

Supplemental Box

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Continuation of:
The previous supplemental box - Box V No 2 (citations and explanations)

Regarding claim 16, Castellani obviates the method according to claim 11, and Castellani further discloses wherein the disease is cystic fibrosis (pg 183, col 1, para 2 - 'Conclusion: Current analytic methods to detect mutations in the CFTR gene ... to extensive scanning/sequencing protocols that enable the detection of novel mutations', wherein 'novel mutations' 'in the CFTR gene' is 'associated with a disease' - 'cystic fibrosis (CF)'; pg 180, col 1 - 'cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene ... have resulted in the identification of more than 1500 CFTR mutations'; Abstract).

Regarding claim 17, Castellani obviates the method according to claim 11, and Castellani further discloses wherein the subject is the subject is Hispanic (pg 182, Table 2 - 'CFTR mutations in selected populations' - col 2 in Table 2, section 3 - 'Hispanic').

Claims 3-4 and 12-13 lack an inventive step under PCT Article 33(3) as being obvious over Castellani, as above, in view of US 2011/0166029 A1 to MARGULIES et al. (hereinafter 'Margulies').

Regarding claim 3, Castellani discloses a method for identifying a novel mutation associated with a disease, the method comprising: obtaining nucleic acid from a subject having a disease; identifying at least one mutation in the nucleic acid; and comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations, and further wherein identifying comprising: sequencing the nucleic acid; and comparing the sequence of the nucleic acid from the sample to a reference sequence, as discussed in the discussion of claim 2.

Castellani does not specifically teach wherein sequencing is sequencing-by-synthesis. Margulies discloses a method for identifying a mutation including a novel mutation associated with a disease (para [0057] - 'methods for identifying mutations correlated with the presence or increased risk of developing an autism spectrum disorder'; para [0059] - 'the methods of the invention for identifying new mutations'), the method comprising: obtaining nucleic acid from a subject having a disease (para [0057] - 'obtaining a nucleic acid sample from a tissue or body fluid sample from a subject having an autism spectrum disorder'; para [0044] - 'obtaining a nucleic acid from a tissue or body fluid sample from a subject and conducting an assay to identify whether there is a variant sequence (i.e., a mutation)'); identifying at least one mutation in the nucleic acid, wherein identifying comprising: sequencing the nucleic acid (para [0057] - 'conducting an assay to identify whether there is a mutation in the nucleic acid sequence in the subject having autism'; para [0059] - 'identifying new mutations, the method may comprise performing the assay ... sequencing)'), and wherein sequencing is performed by sequencing-by-synthesis (para [0048] - 'the sequencing comprises at least one of single-molecule sequencing-by-synthesis'; para [0064] - 'the sequencing comprises at least one of single-molecule sequencing-by-synthesis').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Castellani and Margulies, to obtain a method for identifying a novel mutation associated with a disease, the method comprising: obtaining nucleic acid from a subject having a disease; identifying at least one mutation in the nucleic acid; and comparing the mutation to a database of mutations known to be associated with the disease, wherein mutations that do not match to the database are identified as novel mutations, and further wherein identifying comprising: sequencing the nucleic acid; and comparing the sequence of the nucleic acid from the sample to a reference sequence, based on the teaching of Castellani, and further wherein sequencing is sequencing-by-synthesis, based on the combination of Margulies and Castellani, in order to use the third generation sequence technology for facilitating the identification of a novel mutation with reduced shortcomings of the second-generation sequencing with an increased accuracy (Please see Schadt et al.: pg R231, col 1, last para - 'SMS sequencing by synthesis Single-molecule real-time sequencing. ... is the first TGS approach ... to address many of the shortcomings of SGS', wherein 'SMS' is 'single-molecule sequencing ', 'TGS' is 'third-generation sequencing', and 'SGS' is 'second-generation sequencing (SGS)'; pg R227, col 1 - 'second-generation sequencing (SGS)...a new generation of single-molecule sequencing (SMS) ...sequencing by synthesis (SBS) ... thereby overcoming issues related to the biases introduced by PCR amplification'; pg R227, col 2, middle para - 'third-generation sequencing (TGS)'; pg R230, Table 1).

Regarding claim 4, the combination of Castellani and Margulies discloses the method according to claim 3, and Margulies further discloses wherein sequencing-by-synthesis is single molecule sequencing-by-synthesis (para [0059] - 'identifying new mutations, the method may comprise performing the assay ... sequencing'; para [0048] - 'the sequencing comprises at least one of single-molecule sequencing-by-synthesis'; para [0064] - 'the sequencing comprises at least one of single-molecule sequencing-by-synthesis).

**********Continued in the next supplemental box**********

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/55362

Supplemental Box

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Regarding claim 12, Castellani discloses a method for identifying a novel mutation associated with a disease, the method comprising: obtaining nucleic acid from a subject having a disease; sequencing the nucleic acid, as discussed in the discussion of claim 11.

Castellani does not specifically teach wherein sequencing is sequencing-by-synthesis. Margulies discloses a method for identifying a mutation including a novel mutation associated with a disease (para [0057] - 'methods for identifying mutations correlated with the presence or increased risk of developing an autism spectrum disorder'; para [0059] - 'the methods of the invention for identifying new mutations'), the method comprising: obtaining nucleic acid from a subject having a disease (para [0057] - 'obtaining a nucleic acid sample from a tissue or body fluid sample from a subject having an autism spectrum disorder'; para [0044] - 'obtaining a nucleic acid from a tissue or body fluid sample from a subject and conducting an assay to identify whether there is a variant sequence (i.e., a mutation)'); identifying at least one mutation in the nucleic acid, wherein identifying comprising: sequencing the nucleic acid (para [0057] - 'conducting an assay to identify whether there is a mutation in the nucleic acid sequence in the subject having autism'; para [0059] - 'identifying new mutations, the method may comprise performing the assay ... sequencing)'), and wherein sequencing is performed by sequencing-by-synthesis (para [0048] - 'the sequencing comprises at least one of single-molecule sequencing-by-synthesis'; para [0064] - 'the sequencing comprises at least one of single-molecule sequencing-by-synthesis').

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Castellani and Margulies, to obtain a method for identifying a novel mutation associated with a disease, the method comprising: obtaining nucleic acid from a subject having a disease; sequencing the nucleic acid, based on the teaching of Castellani, and further wherein sequencing is sequencing-by-synthesis, based on the combination of Margulies and Castellani, in order to use the third generation sequence technology for facilitating the identification of a novel mutation with reduced shortcomings of the second-generation sequencing with an increased accuracy (Please see Schadt et al.: pg R231, col 1, last para - 'SMS sequencing by synthesis Single-molecule real-time sequencing. ... is the first TGS approach ... to address many of the shortcomings of SGS', wherein 'SMS' is 'single-molecule sequencing ', 'TGS' is 'third-generation sequencing', and 'SGS' is 'second-generation sequencing (SGS)'; pg R227, col 1 - 'econd-generation sequencing (SGS)...a new generation of single-molecule sequencing (SMS) ...sequencing by synthesis (SBS) ... thereby overcoming issues related to the biases introduced by PCR amplification'; pg R227, col 2, middle para - 'third-generation sequencing (TGS)'; pg R230, Table 1).

Regarding claim 13, the combination of Castellani and Margulies discloses the method according to claim 12, and Margulies further discloses wherein sequencing-by-synthesis is single molecule sequencing-by-synthesis (para [0059] - 'identifying new mutations, the method may comprise performing the assay ... sequencing'; para [0048] - 'the sequencing comprises at least one of single-molecule sequencing-by-synthesis'; para [0064] - 'the sequencing comprises at least one of single-molecule sequencing-by-synthesis).

Claims 1-5, 7-8, 11-14, 16-17 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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SIGNATURE

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Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2018-04-27
Name/Print	Thomas C. Meyers	Registration Number	36,989

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	Attorney Docket Number	GSGE-002/04US

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EFS ID:	32467460
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Casey Suda
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Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	27-APR-2018
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Application Type:	Utility under 35 USC 111(a)

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Warnings:					
Information:					
7	Non Patent Literature	ISR_and_Written_Opinion_for_PCTUS2015056037.pdf	1593813 24f55954cea76ec6478fdbe9a707fa6fa23fee3c	no	11
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8	Non Patent Literature	ISRandWOforPCTUS1461138.pdf	1454722 98637d4a97c9773edc6d46ed2c4ebf7fba17079b	no	11
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9	Non Patent Literature	ISR_and_Written_Opinion_for_PCTUS2013033435.pdf	1138854 cd486c4e3be4cfadf530640ad56d5b29357f5c93	no	6
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10	Non Patent Literature	ISR-WO-PCTUS2015049132.pdf	3893637 eebebaa5f0dfd0650d119ac48ad7925793536bbc	no	14
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11	Non Patent Literature	ISR_PCTUS2015050964.pdf	313446 b50002e970dbbd3c0b5b24b22afd147b2e6760e0	no	6
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12	Non Patent Literature	ISR-WO_PCTUS1460256.pdf	468958 c3c733bdfa46eaddee0f791d8a5f97299e1e3c7e	no	9
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13	Non Patent Literature	ISR-WO-PCT-US2016-012286.pdf	719725 e8e0a8f400a92095151aeb3870afafa91375b4c5	no	7
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14	Non Patent Literature	ISR-WO-PCTUS2015045247.pdf	924080 1468279422da38df92163d5053a782948e0a6c5b	no	10
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15	Non Patent Literature	ISRandWOforPCTUS2014060056.pdf	1708234 e1310006d3f6910334fc43b7fec2612931da2606	no	14
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16	Non Patent Literature	ISR_and_Written_Opinion_for_PCTUS2013032885.pdf	543797 d7704b8c2afd752bea6763091828f6b5292ec7a5	no	9
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18	Non Patent Literature	PCTUS2015030366-ISR.pdf	2925167 f22a16048f169bf0f435dd20f0d9bb04ad3e53b5	no	12
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20	Non Patent Literature	29258-166_-_ISRWO.pdf	1582217 46d1eb2f85880dd6407d0de7cbe85c684d241743	no	14
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22	Non Patent Literature	PCTUS1255362_SearchReport.pdf	918900 c55267b9962b6fd9abe576fb4ea42c3242fa53ae	no	15
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23	Non Patent Literature	Isosomppi-2009-MolVis.pdf	2814941 d2e712b0065e61a8fb0a085aa3875d0572ff2807	no	13
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24	Non Patent Literature	Isosomppi-2009-MolVis2.pdf	2812368 a671dc0503eb7e422a7452f60d424aeb40366495	no	13
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26	Non Patent Literature	29168_244US_-_Kambara-1988-BioTechnol_11.pdf	621210 2cf3332011ffb01f16b98f26009ec98f8564df35	no	6
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27	Non Patent Literature	Kennedy-2013-ASHGmtg.pdf	144805 68b3e8e0a071207ea92fa1e57e9ac0acfc670355	no	2
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28	Non Patent Literature	Kerem.pdf	931536 efb6ea83c278304e54fdc9fce448e1317d5ff97f	no	8
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29	Non Patent Literature	Kinde.PDF	432607 b49cbd00d0b1f73c1711d003db146103fbf93071	no	8
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30	Non Patent Literature	Kneen-1998-BiophysJ.pdf	366453 8a1bf7936301e730dd2b2135079ccef48734dc8b	no	9
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31	Non Patent Literature	Koboldt-2009-Bioinformatics.pdf	254477 cc0b2eb9353e9db2cdf2d2a0c89d74924d0e8e95	no	3
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32	Non Patent Literature	Li-2003-EMBOJ.pdf	560612 9f67fffae4b8643ec7174a7d2ddbfc3d0849d6be	no	12
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33	Non Patent Literature	Li-2010-Bioinformatics.PDF	669269 b1aa9d3c3608466e86cd4403d4be46aac4897ade	no	7
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36	Non Patent Literature	Li-2014-JAMIA.pdf	1821202 4ef554bb4dadc938cc63c535325e8364deec188e	no	11
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Information:					

37	Non Patent Literature	Lin-2008-Bioinformatics.pdf	662777 b3f645a0fe765463b471c5a0edd3a48698940be6	no	7
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38	Non Patent Literature	Lin-2010-BMCGenomics.pdf	768720 0de214d3b5850e464c0ceb41eb0165d69ac758f9	no	14
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39	Non Patent Literature	29258_106WO_-_Liu-2012-ePub.pdf	3541398 c34e45f050aa8ea7445f7c68fbbb7ed027a3b0f4	no	12
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40	Non Patent Literature	Llopis-1998-PNAS.pdf	331302 2b2d4fffb6680b1cf3acd89141fed9b8b6cd8853	no	6
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Information:					
41	Non Patent Literature	Ma-2006-JAmSoc.pdf	319616 dfc0bd06c97d08a3f286421e398ad0df20412863	no	15
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Information:					
42	Non Patent Literature	MacArthur-2014-Nature.pdf	165833 5c474c203c526e507aee6fc16bf2ca6e6e587ac2	no	8
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43	Non Patent Literature	Maddalena-2005-GenetMed.pdf	141876 73d5693d54f3c117e97949a0c7c58f8ccf14e6f3	no	13
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44	Non Patent Literature	Malewicz-2010-ProcACM.pdf	220919 16fdc92e07caaf7f961d1940f024128dc0218acd	no	11
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45	Non Patent Literature	McDonnell.pdf	60837 009fc900237fef2078faead37164854d2b87dc4b	no	1
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46	Non Patent Literature	McKenna-2010-GenomeRes.pdf	788350 129c21c36fd1b6da57b0f3fa17774822f0617015	no	7
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47	Non Patent Literature	Meyer-2008-NatProt.pdf	1114172 211daa6923591dd47a33621e034497d3e67fdd0f	no	12
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48	Non Patent Literature	Miesenbock-1998a.pdf	60877 94d158a2236f5d87cdb94a731198801e062b85d5	no	1
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49	Non Patent Literature	Miller-2010-Genomics.pdf	2695395 1e56c4d1143ed58b74eb13a551e76f3a93d4bf47	no	13
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Information:					

51	Non Patent Literature	Mohammed-2012-Bioinformatics.pdf	462222 d68ac1280182c44623a695ed908745a7c1f850d8	no	3
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Information:					
52	Non Patent Literature	Moudrianakis-1965-PNAS.pdf	1325856 c72874d4ac699c7ee27daa5b6cf4374633703e0e	no	8
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53	Non Patent Literature	Munne.pdf	9241389 32025be35dbba0530b0525f16e021464e6ea145c	no	8
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Information:					
54	Non Patent Literature	Nelson-1989-NAR.pdf	949850 8ba6f0209e12c7854fbd99ca21df387af4f479ac	no	8
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55	Non Patent Literature	Nuttle-2013-NM.pdf	2784231 eb6878d4fd3f8d5fcb24635b4e9356ecb4c773cd	no	56
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Information:					
57	Non Patent Literature	O_Roak-2012-SCIENCE.pdf	13002550 f830136149b923ba235d7bb5f9ac741418ce9e01	no	77
Warnings:					
Information:					
		Total Files Size (in bytes):	92694446		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	32469008
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Casey Suda
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	27-APR-2018
Filing Date:	08-AUG-2016
Time Stamp:	19:03:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Okoniewski-2013-Biotechniques.pdf	5257025 3da00d13ec4abd4863e1eb24778a8e698f4668bb	no	3

Warnings:

Information:					
2	Non Patent Literature	Parkinson.pdf	520769 5b4b74159394 81facd01b1dd9d22b13be76e57c5	no	9
Warnings:					
Information:					
3	Non Patent Literature	Pastor-2010-2010ProcBIOSTEC.pdf	207668 ac26fd1da6e79d4cd9a941b3c25c3100cfbaa198	no	7
Warnings:					
Information:					
4	Non Patent Literature	Paton-2000-Bioinformatics.pdf	4537015 83cfc0e10aa770a750f74f336a8e06fc0e4dcca6	no	10
Warnings:					
Information:					
5	Non Patent Literature	Pinho-2013-Bioinformatics.pdf	963267 954abcc95f6fe30b5122d1f06848d97c4a81cf49	no	8
Warnings:					
Information:					
6	Non Patent Literature	Porreca-2013-ASHGmtg.pdf	162701 df35b09b9cc159107 4f7e5ab3722312271eb21f0	no	2
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7	Non Patent Literature	puregene-handbook-2011.pdf	7116530 a18c08c76b43792090e76ef97c2986ca58bb30e9	no	72
Warnings:					
Information:					
8	Non Patent Literature	Richards-2008-GenetMed.pdf	10248379 71f1950cdc9661ccc7ffd79074361021a46a1438	no	7
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9	Non Patent Literature	Rodriguez-2010-BullAmSoc.pdf	242429 7aaee0f04ee80effba35479ca1e26bcdc314c968	no	11
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10	Non Patent Literature	Schiffman-2009-CancGenCyt.pdf	870335 7fd707d04dead01854a5f88b62b3332bfbff53e6	no	10
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11	Non Patent Literature	Schneeberger-2011-PNAS.pdf	208006 d570cc89e26de029d5434f7e12284f8123b811de	no	6
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12	Non Patent Literature	Schouten.pdf	1112381 2f3699994d4cbef10f36b45a36955f6819622025	no	13
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13	Non Patent Literature	Shen-2013-GenMed.pdf	405483 995fa81efc1f73cf1100b0b9d83d0a5453ec91ab	no	8
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14	Non Patent Literature	Smith-1985-NuclAcidsRes.pdf	1461477 e02f8a8b54df96278808a4cfcd436dd5239b0eb8	no	14
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15	Non Patent Literature	Sproat-1987-NuclAcRes.pdf	1048967 edd4846a40af9fc0d1845e3fde341e2e1a8554b6	no	12
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16	Non Patent Literature	Strom-2005-MutatRes.pdf	686611 4b44dff8cf2a56123b86fef1f9d1772bdd1a5750	no	8
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17	Non Patent Literature	Summerer-2010-GENOMICS.pdf	1000573 0410996fbdc90aad1cad26c44c9dfb9c6494a270	no	6
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18	Non Patent Literature	SESR-14762322.pdf	258509 6d809533899eb3b4a4f19376dd9a9569707a72bd	no	8
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19	Non Patent Literature	Tan-2014-GigaScience.pdf	1064363 aeba9884bed2175fb88b1a1e2c55ae63bdfb7217	no	9
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20	Non Patent Literature	Tkachuk.pdf	646034 833d696ba15d8943673ad4920c3871f28b4f44bd	no	4
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21	Non Patent Literature	Tobler.pdf	937082 fcd02823c959c86e9ce617bf6c3a54d345874388	no	9
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22	Non Patent Literature	Umbarger-2013-ASHGmtg.pdf	151332 f8be1dabb3cbfe5849819409495 3b265d6be9b3	no	2
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23	Non Patent Literature	Umbarger-2014-GenMed.pdf	622377 cb2ae2ae6b12a4e2a7dc679236feb5dbf3b854e1	no	9
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24	Non Patent Literature	Veeneman-2012-BMCBioinformatics.pdf	1122602 c8c11834f06bd911cbf3533fed4830329e5a06eb	no	8
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25	Non Patent Literature	Wallace-1987-MethEnz.pdf	1762524 2e17f2140c8ec9afed4417753cc4057474c47028	no	11
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26	Non Patent Literature	Wang-2005-NAR.pdf	5620018 faece68fde444ced0d9bb7bf2ae8d53b1d1112c6	no	14
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27	Non Patent Literature	Waszak.pdf	7817346 ea652b0deff7a0975ecaafcdd01922c76060c6b9	no	20
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28	Non Patent Literature	Xu-2012-PLoSOne.pdf	578950 bbfef5eeb7ddb3f4bdc9505748550dffc2c1f074	no	6
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29	Non Patent Literature	Ye-2009-Bioinformatics.pdf	3639685 4c5be5e1011489d9b9eb143e0194a3bca4698643	no	7
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30	Non Patent Literature	Yershov.pdf	2169403 4c508766a534413e46703ae0d481df9bf50d2d0b	no	6
Warnings:					
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31	Non Patent Literature	Yoon-2014-NuclAcRes.pdf	1362007 2e86e26d7098222569c815e720dabba63698ebb2	no	9
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32	Non Patent Literature	Zhou-2014-Bioinformatics.pdf	814470 dd4a58e3b2c5f96b58e4408d8b3f4718e2bb621a	no	13
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33	Non Patent Literature	Zuckerman-1987-NuclAcidsRes.pdf	1331481 fd594a38248dee553573220158 34cc0615237036	no	17
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35	Non Patent Literature	pnas00226-0103.pdf	3253510 ba32692afafe04ebd98a0afcd49fb0bb79ce0739	no	8
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		Total Files Size (in bytes):	72016250		

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New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	GSGE-002/04US 29258/78	6709

21710 7590 10/12/2018

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
10/12/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Office Action Summary	Application No. 15/231,687	Applicant(s) Porreca et al.	
	Examiner STEVEN C POHNERT PhD	Art Unit 1634	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/27/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 68-78 and 80-82 is/are pending in the application.

5a) Of the above claim(s) 71-73 and 76-78 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68-70,74-76 and 80-82 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Petitioner Illumina, Inc., EX1003, p. 856

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/27/2018 has been entered.

2. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Claim Status and Formal matters

This action is in response to papers filed 4/27/2018.

Claims 68 has been amended.

Applicant's election without traverse of group I, claims 68-70, 74-75, 80-82 in the reply filed on 3/31/2017 is acknowledged.

Claims 71-73, 76-78 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/31/2017.

Claim 79 has been canceled.

The objection to the specification has been withdrawn in view of the amendment.

The written description rejection has been withdrawn in view of the amendment.

Priority

The instant application was filed 08/08/2016 is a continuation of 13266862, filed 03/13/2012 and is a national stage entry of PCT/US10/01293 , International Filing Date: 04/30/2010, claims priority from provisional application 61182089, claims priority from provisional application 61179358, filed 05/18/2009, claims priority from provisional application 61178923, filed 05/15/2009, and priority from provisional application 61174470, filed 04/30/2009.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 4/27/2018 is being considered by the examiner.

Claim Rejections - 35 USC § 102

4. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

5. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim(s) 68-69, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10)..

With regards to claim 68, Pourmand teaches

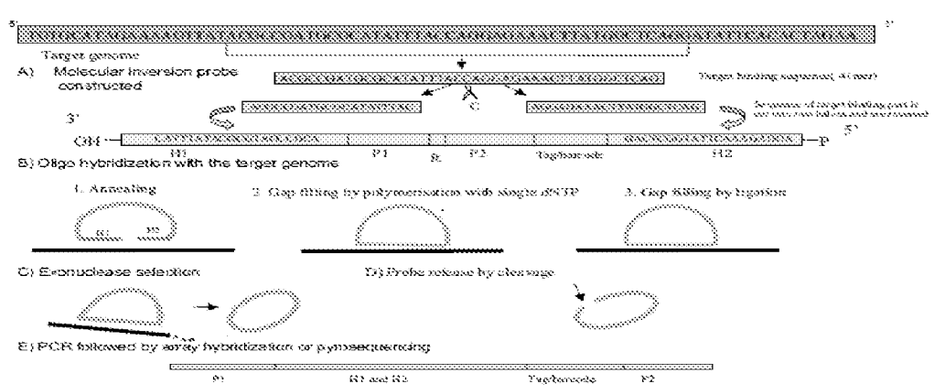


Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from

genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Response to Arguments

The response traverses the rejection asserting, "Pourmand fails to show applying a distinct and unique differentiator tag to each member of a plurality of nucleic acid molecules to generate a plurality of uniquely tagged target nucleic acid molecules..." This argument has been thoroughly reviewed but is not considered persuasive as Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column)..

The response further asserts, "The claimed method uses tags to uniquely identify individual molecules and follow them through the amplification reaction. The method

therefore allows the starting molecules to be distinguished from each other, to overcome bias associated with systematic and random errors in genome capture, amplification, and sequencing.." This argument has been thoroughly reviewed but is not considered persuasive as the response is providing arguments to limitations that are not in the claim. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The response continues by asserting, "While the present claims require uniquely tagging each molecule to generate uniquely tagged target nucleic acid molecules, Pourmand only discloses comparing one group of like-sequences to another, but not for distinguishing from among like-sequences to discern the particular molecule of origin." This argument has been thoroughly reviewed but is not considered persuasive as the response is providing arguments to limitations that are not in the claim. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The response continues by asserting, "The barcodes as reported by Pourmand can distinguish categories of SNPs, but cannot distinguish individual starting molecules. Id., page 2, left column." This argument has been thoroughly reviewed but is not considered persuasive as the response is arguing limitations that are not present in the claims. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., cannot distinguish individual starting molecules. Id., page 2, left column) are not

recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further Pourmand teaches," A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Thus Pourmand could distinguish starting molecules.

The response further asserts, "Since the presently amended claims recite applying a unique differentiator tag to each_ member of a plurality of target nucleic acid molecules to generate uniquely tagged target nucleic acid molecules, which Pourmand does not disclose or suggest, Applicant submits that Pourmand does not anticipate the claims." This argument has been thoroughly reviewed but is not considered persuasive as Pourmand , "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the

probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus the rejection is maintained.

Claim Rejections - 35 USC § 103

7. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

8. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 68-70, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Meyer (Nature Protocoles (2008) volume 3, pages 267-278, epublished Jan 31, 2008).

With regards to claim 68, Pourmand teaches

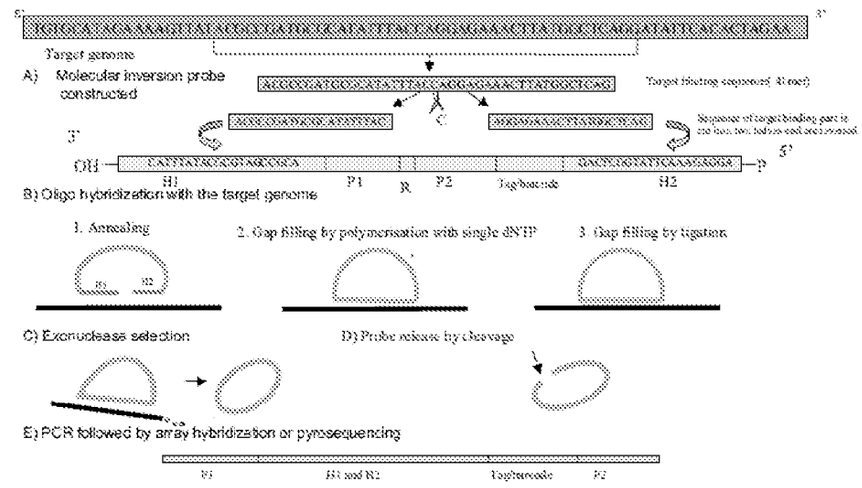


Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV).

These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach determining presence of sequencing or amplification errors.

However, Meyer teaches preparing batches of barcoded nucleic acids (unique tags) by attaching barcodes or sequence tags to nucleic acids. See p. 271, Box 1; Quality control and Procedure. The barcodes are added to purified PCR products or positive control PCR products (p. 272, Reagent Setup; p. 273, step 10). The batches are pooled and sequenced in parallel. A contamination in a batch of barcodes is

determined by determining a frequency at which cross-contamination of adapters occurred during synthesis or dilution. Meyer further teaches a formula that takes into account and estimates false assignment that occurs due to sequencing errors and cross-contamination of barcoding adapters during synthesis and dilution (Box 1). Therefore, Meyer teaches identifying a contamination in a batch of barcodes (unique tags)by determining a frequency at which an incorrect adapter sequence occurs in the batches.

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis. .

Response to Arguments

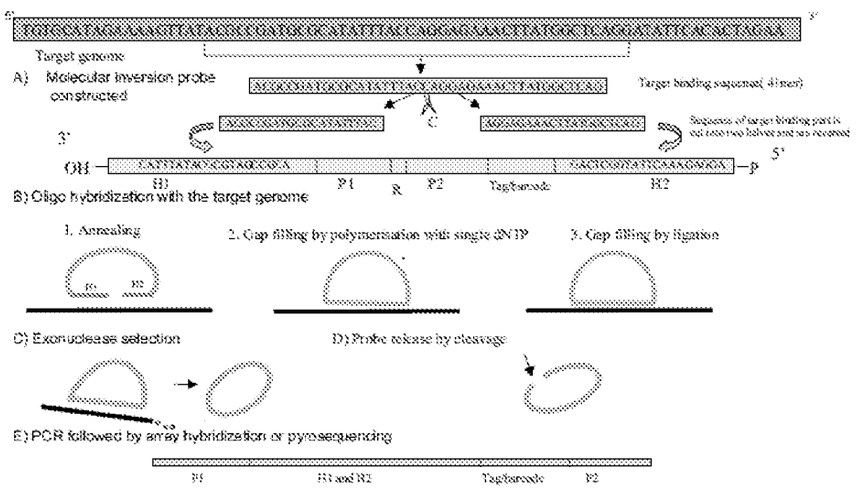
The response begins traversing the rejection by providing arguments with respect to motivation. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385

(2007). In this case, the rejection states, "The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. "

The response continues by asserting the teachings of the Pourmand does not teach all the limitations of the independent claim. This argument has been thoroughly reviewed but is not considered persuasive for the reasons of record.

10. Claim 68-69, 74-75, 80-82 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Shoemaker (US20080090239 published 4/17/2008).

With regards to claim 68, Pourmand teaches



T Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the

amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach use of nucleic acids from circulating tumors or fetal nucleic acids.

However, Shoemaker teaches, "[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large number of maternal cells in the blood which make the analysis time consuming and prone to error."

Shoemaker teaches, "0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying, quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and

imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc."

Shoemaker teaches, "In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods, which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detecting circulating tumor nucleic acids or circulating fetal nucleic acids in the method of Poumard. The artisan would be motivated to use methods that are less invasive methods than aminocentesis or tumor biopsy. The artisan would have a reasonable expectation of success as the artisan is merely using known samples in known methods.

Response to Arguments

The response begins traversing the rejection by providing arguments with respect to motivation. In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or

motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, the rejection states, "The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. "

The response continues by asserting the teachings of the Pourmand does not teach all the limitations of the independent claim. This argument has been thoroughly reviewed but is not considered persuasive for the reasons of record.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

12. Claims 68-70, 74-75, 79-82 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 13/266,862 in view of Pourmand (BMC informatics (2006) volume 7:500, pages 1-10). This is a provisional nonstatutory double patenting rejection.

Claim 1 of '862 is drawn to A method for analyzing a target nucleic acid, the method comprising:providing a sample comprising a target nucleic acid;contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes, each different molecular inversion probe comprising:a 5' region comprising a 5' terminal nucleotide;a 3' region comprising a 3' terminal nucleotide; anda central region flanked by the 5' region and the 3' region;wherein the 5' region ~~re~~ is complementary to anucleic acid residueflanking ~~the~~ a 3' end of one of a plurality of subregions of the target nucleic acid and the 3' region is complementary to a nucleic acid residue flanking a 5' end of the subregion;wherein each subregion is different and overlaps with at least one other subregion; andwherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence;wherein when hybridized to the target nucleic acid in a circular configuration, the 5' terminal nucleotide and the 3' terminal nucleotide of each probe are separated by a plurality of nucleotides on the target nucleic acid; converting hybridized probes into closed circularized probes;isolating a plurality of circularized probes having nucleic acid sequences of different subregions; and analyzing the isolated subregions.

Claim 13 of '862 teach, "wherein the obtaining comprises capturing target nucleic acids from a genomic sample of the subject with molecular inversion probes, each comprising a unique differentiator tag sequence."

Claims of '862 do not specifically teach amplifying.

However, Pourmand teaches

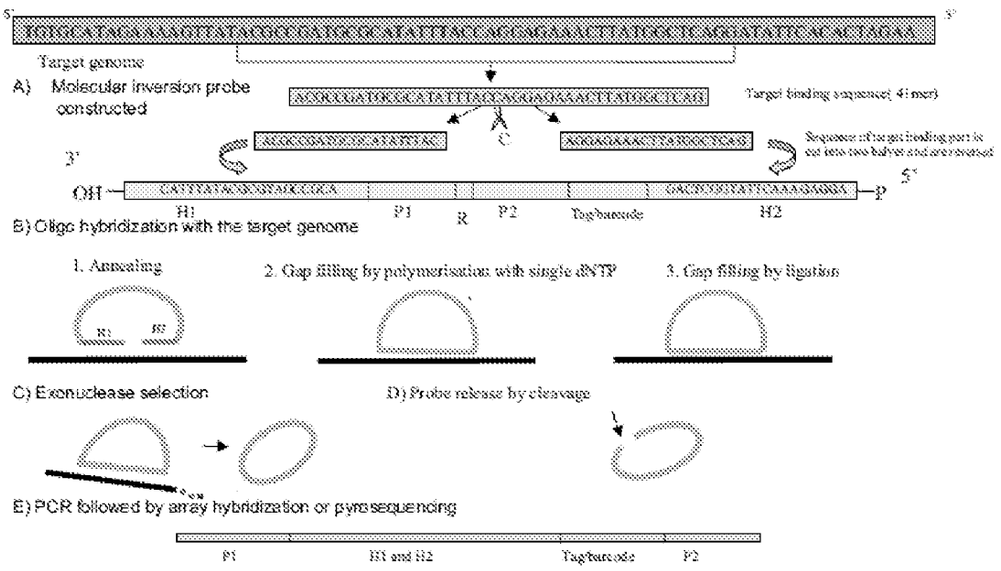


Figure 1

Poumard teaches, “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Other dependent claims are obvious variants of the methods of Pourmand and '862.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to improve the molecular inversion probe method of '862 with unique differentiator tags with amplifying and sequencing of Poumard. The artisan

would be motivated to amplify and sequence the molecular inversion probes to increase the amount of nucleic acid being detected and thus increase the sensitivity by an art . The artisan would have a reasonable expectation of success as the artisan is merely be using art accepted methods of analysis of nucleic acid sequences using molecular inversion probes.

Response to Arguments

The response request the ODP rejection be held in abeyance. Thus the rejection is maintained.

Summary

No claims are allowed.

Akhras (PLOS one (2007) volume 2, e2230) is a reference that may be of interest.

Conclusion

13. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C POHNERT PhD whose telephone number is (571)272-3803. The examiner can normally be reached on Monday- Friday about 6:00 AM-5:30 PM, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven Pohnert/
Primary Examiner, Art Unit 1634

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

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	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US 29258/78

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/SP/	46	International Search Report and Written Opinion for PCT/US12/29790, mailed June 14, 2012 17 pages	
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/SP/	48	International Search Report and Written Opinion for international application no. PCT/US13/62842 with international filing date 1 October 2013, ISR/WO mailed 4 February 2014 (10 pages)	
/SP/	49	International Search Report and Written Opinion for PCT/US13/61691 mailed January 10, 2014 (10 pages)	
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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2018-04-27
Name/Print	Thomas C. Meyers	Registration Number	36,989

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/SP/	1	International Search Report and Written Opinion for PCT/US2013/044039 mailed 01 November 2013, (15 pages)	☐
/SP/	2	International Search Report and Written Opinion for PCT/US2015/056037 mailed 12/23/15; 11 pages	☐
/SP/	3	International Search Report and Written Opinion issued January 29, 2015 in counterpart PCT Application No. PCT/US14/61138	☐
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/SP/	6	Okoniewski, 2013, Precise breakpoint localization of large genomic deletions using PacBio and Illumina next-generation sequencers, Biotechniques 54(2):98-100	☐
/SP/	7	Parkinson, 2012, Preparation of high-quality next-generation sequencing libraries from picogram quantities of target DNA, Genome Res 22:125-133	☐
/SP/	8	Pastor, 2010, Conceptual modeling of human genome mutations: a dichotomy between what we have and what we shoudl have, 2010 Proc BIOSTEC Bioinformatics, pp: 160-166	☐
/SP/	9	Paton, 2000, Conceptual modelling of genomic information, Bioinformatics 16(6):548-57	☐
/SP/	10	Pinho, 2013, MFCompress: a compression tool for FASTA and multi-FASTA data, Bioinformatics 30(1):117-8	☐
/SP/	11	Porreca, 2013, Analytical performance of a Next-Generation DNA sequencing-based clinical workflow for genetic carrier screening, American Society of Human Genetics 63rd Annual Meeting, Abstract, October 22, 2013	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US

/SP/	12	Qiagen, 2011, Gentra Puregene handbook, 3d Ed. (72 pages)	☐
/SP/	13	Richards, 2008 ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions, Genet Med 10(4):294-300	☐
/SP/	14	Rodriguez, 2010, Constructions from Dots and Lines, Bull Am Soc Inf Sci Tech 36(6):35-41	☐
/SP/	15	Schiffman, 2009, Molecular inversion probes reveal patterns of 9p21 deletion and copy number aberrations in childhood leukemia, Cancer Genetics and Cytogenetics 193:9-18.	☐
/SP/	16	Schneeberger, 2011, Reference-guided assembly of four diverse Arabidopsis thaliana genomes, PNAS 108 (25):10249-10254	☐
/SP/	17	Schouten, 2002, Relative Quantification of 40 Nucleic Acid Sequences by Multiplex Ligation-Dependent Probe Amplification, Nucle Acids Res 30 (12):257	☐
/SP/	18	Shen, 2013, Multiplex capture with double-stranded DNA probes, Genome Medicine 5(50):1-8	☐
/SP/	19	Smith, 1985, The synthesis of oligonucleotides containing an aliphatic amino group at the 5' terminus: synthesis of fluorescent DNA primers for use in DNA sequence analysis, Nucl. Acid Res., 13:2399-2412	☐
/SP/	20	Smith, 2010, Highly-multiplexed barcode sequencing: an efficient method for parallel analysis of pooled samples, Nucleic Acids Research 38(13):e142 (8 pages).	☐
/SP/	21	Sproat, 1987, The synthesis of protected 5'-mercapto-2',5'-dideoxyribonucleoside-3'-O-phosphoramidites; uses of 5'-mercapto-oligodeoxyribonucleotides, Nucl Acid Res 15:4837-4848	☐
/SP/	22	Strom, 2005, Mutation detection, interpretation, and applications in the clinical laboratory setting, Mutat Res 573:160-67	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
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	First Named Inventor	Gregory Porreca
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	Attorney Docket Number	GSGE-002/04US

/SP/	23	Summerer, 2010, Targeted High Throughput Sequencing of a Cancer-Related Exome Subset by Specific Sequence Capture With a Fully Automated Microarray Platform, Genomics 95(4):241-246	☐
/SP/	24	Supplementary European search report and opinion dated October 13, 2016, for EP 14762322 (8 pages)	☐
/SP/	25	Tan, 2014, Clinical outcome of preimplantation genetic diagnosis and screening using next generation sequencing, GigaScience 3(30):1-9.	☐
/SP/	26	Tkachuk, 1990, Detection of bcr-abl Fusion in Chronic Myelogeneous Leukemia by in Situ Hybridization, Science 250:559	☐
/SP/	27	Tobler, 2005, The SNPlex Genotyping System: A Flexible and Scalable Platform for SNP Genotyping, J Biomol Tech 16(4):398	☐
/SP/	28	Umbarger, 2013, Detecting contamination in Next Generation DNA sequencing libraries, American Society of Human Genetics 63rd Annual Meeting, Abstract, October 22, 2013	☐
/SP/	29	Umbarger, 2014, Next-generation carrier screening, Gen Med 16(2):132-140	☐
/SP/	30	Veeneman, 2012, Oculus: faster sequence alignment by streaming read compression, BMC Bioinformatics 13:297	☐
/SP/	31	Wallace, 1987, Oligonucleotide probes for the screening of recombinant DNA libraries, Meth Enz 152:432-442	☐
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/04US

/SP/	34	Xu, 2012, FastUniq: A fast de novo duplicates removal tool for paired short reads, PLoS One 7(12):e52249	☐
/SP/	35	Ye, 2009, Pindel: a pattern growth approach to detect break points of large deletions and medium size insertions from paired-end short reads, Bioinformatics 25(21):2865-2871	☐
/SP/	36	Yershov, 1996, DNA analysis and diagnostics on oligonucleotide microchips, PNAS 93:4913-4918	☐
/SP/	37	Yoon, 2014, MicroDuMIP: target-enrichment technique for microarray-based duplex molecular inversion probes, Nucl Ac Res 43(5):e28	☐
/SP/	38	Zhou, 2014, Bias from removing read duplication in ultra-deep sequencing experiments, Bioinformatics 30 (8):1073-1080	☐
/SP/	39	Zuckerman, 1987, Efficient methods for attachment of thiol specific probes to the 3'-ends of synthetic oligodeoxyribonucleotides, Nucl Acid Res 15(13):5305-5321	☐
/SP/	40	Isosomppi, 2009, Disease-causing mutations in the CLRN1 gene alter normal CLRN1 protein trafficking to the plasma membrane, Mol Vis 15:1806-1818	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Steven Pohnert/ (10/04/2018)	Date Considered	10/04/2018

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	34292773
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers
Filer Authorized By:	
Attorney Docket Number:	GSGE-002/04US 29258/78
Receipt Date:	13-NOV-2018
Filing Date:	08-AUG-2016
Time Stamp:	16:31:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	MLB-POA-aia0080-signed.pdf	286732 2f0face4998b8606e1672a8907d08c31f78bc85e	no	2

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	MLB-002-04US_373-STATEMENT.pdf	25896 0e97ce256cc8eb17f490a7cdeb90e45fa740fc7a	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	312628	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/80 (07-17)
Approved for use through 01/31/2018. OMB 0651-0035
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 21710

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 21710

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Molecular Loop Biosolutions, LLC
57 Reservoir Street #1
Cambridge, MA 02138

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature [signature]	Date 11/6/2018
Name Gregory Porreca	Telephone 609 457 4431
Title Managing Member and CEO	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Molecular Loop Biosolutions, LLC

Application No./Patent No.: 15/231,687 Filed/Issue Date: August 8, 2016

Titled: METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Molecular Loop Biosolutions, LLC , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____ , Frame _____ , or for which a copy thereof is attached.

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Gregory Porreca To: Good Start Genetics, Inc.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 042010 , Frame 0781 , or for which a copy thereof is attached.

2. From: Uri Laserson To: Good Start Genetics, Inc.
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: Good Start Genetics, Inc. To: Molecular Loop Biosolutions, LLC
The document was recorded in the United States Patent and Trademark Office at
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The document was recorded in the United States Patent and Trademark Office at
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☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/THOMAS C. MEYERS/	November 13, 2018
Signature	Date
THOMAS C. MEYERS	36,989
Printed or Typed Name	Title or Registration Number

63198202 v1

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

IMPROPER CFR REQUEST

OC000000103863929

Date Mailed: 11/16/2018

RESPONSE TO REQUEST FOR CORRECTED FILING RECEIPT

Power of Attorney, Claims, Fees, System Limitations, and Miscellaneous

In response to your request for a corrected Filing Receipt, the Office is unable to comply with your request because:

- Any request to correct or update the name of the applicant must include an application data sheet (ADS) in compliance with 37 CFR 1.76 specifying the correct or updated name of the applicant in the applicant information section. Any request to change the applicant after an original applicant has been specified under 37 CFR 1.46(b) must include a new ADS in compliance with 37 CFR 1.76 specifying the applicant in the applicant information section and comply with 37 CFR 3.71 and 3.73. See 37 CFR 1.46(c).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/qtran/

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15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10

CONFIRMATION NO. 6709

IMPROPER CPOA LETTER

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

OC000000103863866

Date Mailed: 11/16/2018

NOTICE REGARDING POWER OF ATTORNEY

This is in response to the power of attorney filed 11/13/2018. The power of attorney in this application is not accepted for the reason(s) listed below:

- The power of attorney has not been accepted because the party who is giving power has not been identified. Power of attorney may only be signed by the applicant for patent (37 CFR 1.42) or the patent owner. A party who is not the applicant must become the applicant in accordance with 37 CFR 1.46(c) and appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. For a reissue application, reexamination proceeding, or supplemental examination proceeding, a patent owner who was not the applicant under 37 CFR 1.46 must appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. See 37 CFR 1.32(b)(4).

/qtran/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 11/23/2018

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/23/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Applicant-Initiated Interview Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) STEVEN C. POHNERT PhD.

(3) Annie Cook.

(2) Thomas Meyers.

(4) Greg Porecca.

Date of Interview: 15 November 2018.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☑102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 68.

Identification of prior art discussed: Pourmand.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The discussion began with what applying a unique differentiator tag required. The examiner indicated the molecular inversion probes of Pourmand did apply unique tags to the sequences. Continued discussion revealed the intent of the claim is was to apply unique barcodes or something similar by ligation or similar means. The examiner and representative agreed that both interpretations were within the scope of the claims. The examiner suggested amending the claim to differentiate the claims from the teachings of Pourmand. The examiner agreed to review a proposed claim amendment. The examiner also suggested that filing an after final would be another way to do get review of the claim and minimize the chance of first action final. NO agreement on patentability was reached..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

	/Steven Pohnert/ Primary Examiner, Art Unit 1634

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Electronic Acknowledgement Receipt	
EFS ID:	34450824
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers
Filer Authorized By:	
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	05-DEC-2018
Filing Date:	08-AUG-2016
Time Stamp:	10:00:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		MLB-002-04US_RESPONSE-REQUEST.pdf	46846 62e7009a7d319d091394dad6ea4a971b1f6c20fe	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response After Final Action	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	8

Warnings:					
Information:					
2	After Final Consideration Program Request	sb0434.pdf	213664 344bd874bfe0dc75bf01c00f0e859303e389118d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	260510		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT WITH AFCP 2.0 REQUEST

This paper is in response to a final Office Action mailed October 12, 2018, from the United States Patent and Trademark Office. Applicant submits herewith a Certification and Request under the After Final Consideration Pilot Program 2.0.

Applicant believes no fee is due with this paper. Nevertheless, Applicant authorizes any and all required fees due with this response to be charged to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 5.

Amendments to the claims

Please amend the claims as follows. The following listing of claims will replace all prior versions of claims in the application.

1-67. (Canceled)

68. (Currently Amended) A method for nucleic acid identification, the method comprising the steps of:

tagging each independently isolated target nucleic acid molecule ~~applying a unique differentiator tag to each member~~ of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag to generate a plurality of uniquely tagged target nucleic acid molecules;

amplifying said uniquely tagged target nucleic acid molecules to generate amplicons that contain the uniquely tagged target nucleic acid molecules;

sequencing the amplicons obtained in said amplifying step, wherein each unique differentiator tag is sequenced along with the target nucleic acid molecule; and

identifying a sequence for said nucleic acid molecules.

69. (Previously Presented) The method of claim 68, wherein said identifying step comprises identifying said unique differentiator tags.

70. (Previously Presented) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon the number of said unique differentiator tags.

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71. (Withdrawn) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

72. (Withdrawn) The method of claim 71, wherein said common identifier is used to identify a sample source.

73. (Withdrawn) The method of claim 72, wherein said common identifier is used to identify a patient.

74. (Previously Presented) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (Previously Presented) The method of claim 68, wherein said plurality of nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (Withdrawn) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

77. (Withdrawn) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

78. (Withdrawn) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

79. (Canceled)

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80. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are circulating tumor nucleic acid molecules.

81. (Previously Presented) The method of claim 68, further comprising the step of determining the copy number of a genomic region or transcript in a patient from whom the sample is obtained.

82. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are maternally-circulating fetal or placental nucleic acid molecules.

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Remarks

Claims 68-78 and 80-82 are pending in the application. Claim 68 is amended. Claims 1-68 and 79 were previously canceled. Claims 71-73 and 76-78 were previously withdrawn. Support for the claim amendments is found throughout the as-filed application, including at pages 40-42. No new matter is added.

Examiner Interview

Applicant thanks the Examiner for his time and consideration in conducting the telephonic interview on November 13, 2018. The pending claims and Pourmand (BMC Informatics, 2006, 7:500) were discussed in the interview. Applicant submits the claim amendments filed herewith provide clarification of the invention.

Rejection under 35 U.S.C. §102

The Office Action states that claims 68, 69, 74, 75, and 81 are rejected under 35 U.S.C. §102(b) over Pourmand.

Applicant respectfully submits that Pourmand does not anticipate the present claims because Pourmand does not disclose each and every element of the amended claims.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. M.P.E.P. §2131.

Amended claim 68 recites tagging each independently isolated target nucleic acid molecule of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag. For instance, the individual target nucleic acid molecules in the present invention may have been isolated in a reaction or vessel, but each molecule is tagged with a different, unique differentiator tag. The resulting molecules are amplified to generate amplicons that contain the uniquely tagged target nucleic acid molecules. Those amplicons are sequenced, and each unique differentiator tag is sequenced along with the target nucleic acid molecule.

Each target nucleic acid in the present invention is tagged with a unique differentiator tag, and the unique differentiator tags follow the target molecules through the amplification and sequencing steps. Thus, the present invention allows the starting molecules to be distinguished from each other to overcome bias associated with systematic and random errors in genome capture, amplification, and sequencing. *See application as-filed, page 8.* By providing unique differentiator tags for each target nucleic acid that follow the target through the amplifying and sequencing steps, the invention allows each starting target nucleic acid to be identified.

Pourmand merely shows methods for designing barcoded molecular inversion probes (MIPs) that can detect SNPs. *See Pourmand, page 4, first column, last paragraph, through second column, first paragraph.* The barcodes are not designed to differentiate the particular starting molecule from all other molecules. Pourmand simply applies tags, amplifies, and then observes the relative numbers of one SNP versus another. Unlike the present claims where every starting molecule has a different tag, Pourmand merely provides an identifier of the MIP that hybridized the target. Therefore, Pourmand cannot accomplish the goal of minimizing bias because Pourmand does not allow individual starting molecules to be distinguished.

Applicant submits that Pourmand does not anticipate independent claim 68 because Pourmand does not disclose tagging each independently isolated target nucleic acid molecule of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag. Dependent claims 69, 74, 75, and 81 are not anticipated for at least the same reasons as claim 68. Accordingly, the §102 rejection is overcome.

Rejections under 35 U.S.C. §103

The Office Action states that claims 68-70, 74, 75, and 81 are rejected under 35 U.S.C. §103 over Pourmand in view of Meyer (Nat. Prot., 2008, 3:267-78). The Office Action states that claims 68, 69, 74, 75, and 80-82 are rejected under 35 U.S.C. §103 over Pourmand in view of

Shoemaker (US 2008/0090239). Applicant submits that the claims are not obvious over any combination of those references.

In order to establish a prima facie case of obviousness, the prior art must provide motivation to modify a reference or to combine multiple references in a manner that would lead one of ordinary skill in the art to an applicant's claimed invention with a reasonable expectation of success. *See e.g., KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); and MPEP § 2143. Furthermore, an obviousness rejection cannot be established unless each claim element is disclosed in the cited art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Without a reference disclosing the missing claim elements, there can be no motivation of achieving the claimed invention or likelihood of success in doing so. *See Wyers v. Master Lock Co.*, 616 F.3d 1231 (Fed. Cir. 2010) (providing a prima face case requires a teaching or suggestion of all claim limitations along with an apparent reason to combine the references).

As discussed in the section above, Pourmand fails to disclose each and every claim element. Meyer and Shoemaker do not make up for the deficiencies of Pourmand.

Meyer merely reports a molecular barcoding method for sequencing multiple samples on the 454 platform. *See Meyer, Abstract.* Meyer does not disclose using MIPs to generate uniquely tagged target nucleic acid molecules. Shoemaker reports the use of nucleic acids from circulating tumor samples and fetal samples. *Shoemaker, paragraph [0004].* Shoemaker does not disclose or suggest applying a unique differentiator tag to each target nucleic acid to generate uniquely tagged molecules that can be used to identify amplicons. As with Pourmand, neither Meyer nor Shoemaker discloses the element of applying a unique differentiator tag to each independently isolated nucleic acid molecule to generate a plurality of uniquely tagged target nucleic acid molecules. Accordingly, no combination of those references makes the present claims obvious.

Applicant submits that the §103 rejection is overcome and should be withdrawn.

Double Patenting

Claims 68-70, 74, 75, and 79-82 are provisionally rejected on the ground of nonstatutory double patenting over claim 1 of co-pending Application No. 13/266,862 in view of Pourmand. Since the rejection is provisional, Applicant requests that it be held in abeyance.

Conclusion

If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: December 5, 2018

Respectfully submitted,
BROWN RUDNICK LLP

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63199520 v1

Petitioner Illumina, Inc., EX1003, p. 933

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
MLB-002/04US 34468/10	15/231,687	August 8, 2016
First Named Inventor:	**Title:**	
Gregory Porreca	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
    - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
    - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
        - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
        - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
            - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
            - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/Thomas C. Meyers/	December 5, 2018
Name (Print/Typed) Thomas C. Meyers	**Practitioner Registration No.** 36989

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☐ * Total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Examiner-Initiated Interview Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA Status** No

All participants (applicant, applicant's representative, PTO personnel):

(1) STEVEN C. POHNERT PhD. (3) _____.

(2) THomas Meyers. (4) _____.

Date of Interview: 11 December 2018.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☑ 102 ☑ 103 ☐ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 68.

Identification of prior art discussed: cited.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The examiner contacted the representative to indicate the amendment could not be reviewed in the time allotted. Thus the amendment would be treated under pre-pilot practice and would not be entered..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Steven Pohnert/
Primary Examiner, Art Unit 1634

Petitioner Illumina, Inc., EX1003, p. 936

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 12/17/2018

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/17/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA Status** No

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 December 2018 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☑ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires ____ months from the mailing date of the final rejection.
   b) ☑ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection.The current period for reply expires ____ months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANTS FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37CFR 41.37(a).

AMENDMENTS

3. ☑ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☑ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☑ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: See continuation sheet (See 37CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicants reply has overcome the following rejection(s): _____
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☑ For purposes of appeal, the proposed amendment(s):(a) ☑ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☐ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☑ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation sheet.
13. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
14. ☑ Other: 413b and 2323.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed:_____.
    Claim(s) objected to:_____.
    Claim(s) rejected:68-70,74-76 and 80-82.
    Claim(s) withdrawn from consideration:71-73 and 76-78.

	/Steven Pohnert/ Primary Examiner, Art Unit 1634

Petitioner Illumina, Inc., EX1003, p. 938

Attachment to Advisory

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

AFCP2.0

Applicant's request for entry into AFCP 2.0 is acknowledged, but is denied because the response cannot be reviewed and a search conducted in the limited amount of time authorized for this pilot program. Therefore, the response is being reviewed under pre-pilot practice.

Continuation of box 3: The amendments filed on 12/5/2018 further limit the claims to, “tagging each independently isolated target nucleic acid molecule,” “a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag to generate a plurality of uniquely tagged target nucleic acid molecules; ” “to generate amplicons that contain the uniquely tagged target nucleic acid molecules; sequencing the amplicons obtained in said amplifying step, wherein each unique differentiator tag is sequenced along with the target nucleic acid molecule. “ These new limitations further limit the scope of the claims and thus require further search and consideration because the claims now require additional elements.

MPEP 714.13 states, " It should be kept in mind that applicant cannot, as a matter of right, amend any finally rejected claims, add new claims after a final rejection (see 37 CFR 1.116) or reinstate previously canceled claims. Except where an amendment merely cancels claims, adopts examiner suggestions, removes issues for appeal, or in some other way requires only a cursory review by the examiner,

compliance with the requirement of a showing under 37 CFR 1.116(b)(3) is expected in all amendments after final rejection."

The newly amended claims require "tagging each independently isolated target nucleic acid molecule," "a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag to generate a plurality of uniquely tagged target nucleic acid molecules; " "to generate amplicons that contain the uniquely tagged target nucleic acid molecules; sequencing the amplicons obtained in said amplifying step, wherein each unique differentiator tag is sequenced along with the target nucleic acid molecule;. This is a new limitation that has not previously been presented and thus would require a new search.

Continuation of box 12:

The response traverses the 102 and 103 rejection in view of the amendments. These arguments have been thoroughly reviewed but are not considered persuasive in view of non-entry of the amendment.

The response further asserts, "Pourmand merely shows methods for designing barcoded molecular inversion probes (MIPs) that can detect SNPs. See Pourmand, page 4, first column, last paragraph, through second column, first paragraph. The barcodes are not designed to differentiate the particular starting molecule from all other molecules. Pourmand simply applies tags, amplifies, and then observes the relative numbers of one SNP versus another. Unlike the present claims where every starting molecule has a different tag, Pourmand merely provides an identifier of the MIP that hybridized the target. Therefore, Pourmand cannot accomplish the goal of minimizing bias because Pourmand does not allow individual starting molecules to be

distinguished." This argument has been thoroughly reviewed but is not considered persuasive as the response is arguing limitations that are not present in the claim.

The response request the ODP rejection be held in abeyance as the rejection is provisional. This argument is not persuasive as until the ODP rejection is addressed the application will not be allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C POHNERT PhD whose telephone number is (571)272-3803. The examiner can normally be reached on Monday- Friday about 6:00 AM-5:30 PM, every second Friday off, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-07311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven Pohnert/
Primary Examiner, Art Unit 1634

AFCP 2.0 Decision

Application No.	Applicant(s)	
15/231,687	Porreca et al.	
Examiner	**Art Unit**	**AIA Status**
STEVEN C POHNERT PhD	1634	No

This is in response to the After Final Consideration Pilot request filed 05 December 2018.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

   ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.

   ☐ A non-broadening amendment to at least one independent claim was not submitted.

   ☐ A proper AFCP 2.0 request was submitted in response to the most recent final rejection.

   ☐ Other: _____

2. **Proper Request**

   A. After final amendment submitted with the request will not be treated under AFCP 2.0.
   The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

   ☑ The after final amendment will be treated under pre-pilot procedure.

   B. Updated search and/or completed additional consideration.
   The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

   ☐ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.

   ☐ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action . See attached interview summary for further details.

   ☐ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.

   ☐ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.

   ☐ 5. Other: _____

   Examiner Note: Please attach an interview summary when necessary as described above.

Petitioner Illumina, Inc., EX1003, p. 943

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 12/19/2018

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/19/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Applicant-Initiated Interview Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) STEVEN C. POHNERT PhD. (3) _____.

(2) Annie Cook. (4) _____.

Date of Interview: 12 December 2018.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☑Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 68.

Identification of prior art discussed: none.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The representative called about the status of the case, as they can see an interview summary in PAIR indicating the amendments taking more time than given under AFCP2.0 and thus being treated under pre-pilot practices. The examiner indicated, that he did leave a message to that effect and put in the interview summary as part of the advisory action. The examiner indicated the advisory action should hopefully be mailed within a week. No agreement on patentability occurred..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

	/Steven Pohnert/ Primary Examiner, Art Unit 1634

Petitioner Illumina, Inc., EX1003, p. 945

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Electronic Acknowledgement Receipt

EFS ID:	34670144
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers
Filer Authorized By:	
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	21-DEC-2018
Filing Date:	08-AUG-2016
Time Stamp:	14:04:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	MLB-POA-aia0080-signed.pdf	286732 2f0face4998b8606e1672a8907d08c31f78bc85e	no	2

Warnings:

Information:					
2	Assignee showing of ownership per 37 CFR 3.73	MLB-002-04US_373Statement.pdf	27918 6fac298efbc13f120cd096ffb9dc5d3ee50b54f4	no	2
Warnings:					
Information:					
3	Application Data Sheet	MLB-002-04US_Updated-ADS.pdf	27654 8b3d33940af36cfd772fe30ff31fa4549a2c56c5	no	5
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
		Total Files Size (in bytes):	342304		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/80 (07-17)
Approved for use through 01/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person is required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 21710

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 21710

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Molecular Loop Biosolutions, LLC
57 Reservoir Street #1
Cambridge, MA 02138

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature [signature]	Date 11/6/2018
Name Gregory Porreca	Telephone 609 457 4431
Title Managing Member and CEO	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Molecular Loop Biosolutions, LLC

Application No./Patent No.: 15/231,687 Filed/Issue Date: August 8, 2016

Titled: METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Molecular Loop Biosolutions, LLC , a Limited Liability Company
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____ , Frame _____ , or for which a copy thereof is attached.

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Gregory Porreca To: Good Start Genetics, Inc.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 042010 , Frame 0781 , or for which a copy thereof is attached.

2. From: Uri Laserson To: Good Start Genetics, Inc.
   The document was recorded in the United States Patent and Trademark Office at
   Reel 042010 , Frame 0781 , or for which a copy thereof is attached.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: Good Start Genetics, Inc. To: Molecular Loop Biosolutions, LLC
The document was recorded in the United States Patent and Trademark Office at
Reel 047459 , Frame 0461 , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Thomas C. Meyers/	December 21, 2018
Signature	Date
Thomas C. Meyers	36,989
Printed or Typed Name	Title or Registration Number

63250358 v1

Corrected Application Data Sheet

Inventor Information

Inventor Number::	1
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State or Province of Residence::	MA
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Petitioner Illumina, Inc., EX1003, p. 953

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Country of mailing address::	US
Postal or Zip Code of mailing address::	02215

Correspondence Information

Correspondence Customer Number::	21710
E-Mail address::	ip@brownrudnick.com

Application Information

Application Number::	15/231,687
Filing Date::	08/08/16
Application Type::	Regular
Subject Matter::	Utility
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
Attorney Docket Number::	~~GSGE-002/04US 29258/78~~ MLB-002/04US 34468/10
Request for Early Publication?::	No
Request for Non-Publication?::	Yes
Total Drawing Sheets::	16

Petitioner Illumina, Inc., EX1003, p. 954

Small Entity?::	Yes
Petition included?::	No
Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2::	No
This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013::	No

Representative Information

Representative Customer Number::	21710

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::	Prior Appl Status::
This Application	Continuation of	13/266862	03/13/12	Pending
13/266862	a 371 of international	PCT/US2010/001293	04/30/10	Expired
PCT/US2010/001293	Claims benefit of provisional	61/182089	05/28/09	Expired
PCT/US2010/001293	Claims benefit of provisional	61/179358	05/18/09	Expired
PCT/US2010/001293	Claims benefit of provisional	61/178923	05/15/09	Expired
PCT/US2010/001293	Claims benefit of provisional	61/174470	04/30/09	Expired

Foreign Priority Information

Applicant Information

Applicant Number::	1
Organization Name::	~~Good Start Genetics, Inc.~~ Molecular Loop Biosolutions, LLC
Street of mailing address::	~~237 Putnam Avenue~~ 57 Reservoir Street #1
City of mailing address::	Cambridge
State or Province of mailing address::	MA
Country of mailing address::	US
Postal or Zip Code of mailing address::	~~02139~~ 02138

Petitioner Illumina, Inc., EX1003, p. 956

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).** This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants. See 37 CFR 1.4(d) for the manner of making signatures and certifications.			
Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2018-12-21
Name	Thomas C. Meyers	Registration Number	36,989

63250348 v1

Petitioner Illumina, Inc., EX1003, p. 957

Electronic Acknowledgement Receipt	
EFS ID:	34689424
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers
Filer Authorized By:	
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	26-DEC-2018
Filing Date:	08-AUG-2016
Time Stamp:	12:02:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$950
RAM confirmation Number	122618INTEFSW00021656500369
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		MLB-002-04US_RESPONSE.pdf	46833 8c1c6454e3009ea3d25b3a3533877d0e320f9f52	yes	8
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment Submitted/Entered with Filing of CPA/RCE		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	8	
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	MLB-002-04US-RCE.pdf	1354572 470bb22793c7b0497b75af1bd8412bc1c11ee4c0	no	3
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30648 593956713ef685ade3f43480a5fa14dfb08cf404	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1432053		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT WITH

REQUEST FOR CONTINUED EXAMINATION

This paper is in response to a final Office Action mailed October 12, 2018 and an Advisory Action mailed December 17, 2018, from the United States Patent and Trademark Office. Applicant submits herewith a Request for Continued Examination and requisite fees.

Applicant believes no additional fees are due with this paper. Nevertheless, Applicant authorizes any and all required fees due with this response to be charged to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 5.

Amendments to the claims

Please amend the claims as follows. The following listing of claims will replace all prior versions of claims in the application.

1-67. (Canceled)

68. (Currently Amended) A method for nucleic acid identification, the method comprising the steps of:

tagging each independently isolated target nucleic acid molecule ~~applying a unique differentiator tag to each member~~ of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag to generate a plurality of uniquely tagged target nucleic acid molecules;

amplifying said uniquely tagged target nucleic acid molecules to generate amplicons that contain the uniquely tagged target nucleic acid molecules;

sequencing the amplicons obtained in said amplifying step, wherein each unique differentiator tag is sequenced along with the target nucleic acid molecule; and

identifying a sequence for said nucleic acid molecules.

69. (Previously Presented) The method of claim 68, wherein said identifying step comprises identifying said unique differentiator tags.

70. (Previously Presented) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon the number of said unique differentiator tags.

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71. (Withdrawn) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

72. (Withdrawn) The method of claim 71, wherein said common identifier is used to identify a sample source.

73. (Withdrawn) The method of claim 72, wherein said common identifier is used to identify a patient.

74. (Previously Presented) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (Previously Presented) The method of claim 68, wherein said plurality of nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (Withdrawn) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

77. (Withdrawn) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

78. (Withdrawn) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

79. (Canceled)

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80. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are circulating tumor nucleic acid molecules.

81. (Previously Presented) The method of claim 68, further comprising the step of determining the copy number of a genomic region or transcript in a patient from whom the sample is obtained.

82. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are maternally-circulating fetal or placental nucleic acid molecules.

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Remarks

Claims 68-78 and 80-82 are pending in the application. Claim 68 is amended. Claims 1-67 and 79 were previously canceled. Claims 71-73 and 76-78 were previously withdrawn. Support for the claim amendments is found throughout the as-filed application, including at pages 40-42. No new matter is added.

Examiner Interview

Applicant thanks the Examiner for his time and consideration in conducting the telephonic interview on November 13, 2018. The pending claims and Pourmand (BMC Informatics, 2006, 7:500) were discussed in the interview. Applicant submits the claim amendments filed herewith provide clarification of the invention.

Rejection under 35 U.S.C. §102

The Office Action states that claims 68, 69, 74, 75, and 81 are rejected under 35 U.S.C. §102(b) over Pourmand.

Applicant respectfully submits that Pourmand does not anticipate the present claims because Pourmand does not disclose each and every element of the amended claims.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. M.P.E.P. §2131.

Amended claim 68 recites tagging each independently isolated target nucleic acid molecule of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag. For instance, the individual target nucleic acid molecules in the present invention may have been isolated in a reaction or vessel, but each molecule is tagged with a different, unique differentiator tag. The resulting molecules are amplified to generate amplicons that contain the uniquely tagged target nucleic acid molecules. Those amplicons are sequenced, and each unique differentiator tag is sequenced along with the target nucleic acid molecule.

Each target nucleic acid in the present invention is tagged with a unique differentiator tag, and the unique differentiator tags follow the target molecules through the amplification and sequencing steps. Thus, the present invention allows the starting molecules to be distinguished from each other to overcome bias associated with systematic and random errors in genome capture, amplification, and sequencing. *See application as-filed, page 8.* By providing unique differentiator tags for each target nucleic acid that follow the target through the amplifying and sequencing steps, the invention allows each starting target nucleic acid to be identified.

Pourmand merely shows methods for designing barcoded molecular inversion probes (MIPs) that can detect SNPs. *See Pourmand, page 4, first column, last paragraph, through second column, first paragraph.* The barcodes are not designed to differentiate the particular starting molecule from all other molecules. Pourmand simply applies tags, amplifies, and then observes the relative numbers of one SNP versus another. Unlike the present claims where every starting molecule has a different tag, Pourmand merely provides an identifier of the MIP that hybridized the target. Therefore, Pourmand cannot accomplish the goal of minimizing bias because Pourmand does not allow individual starting molecules to be distinguished.

Applicant submits that Pourmand does not anticipate independent claim 68 because Pourmand does not disclose tagging each independently isolated target nucleic acid molecule of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag. Dependent claims 69, 74, 75, and 81 are not anticipated for at least the same reasons as claim 68. Accordingly, the §102 rejection is overcome.

Rejections under 35 U.S.C. §103

The Office Action states that claims 68-70, 74, 75, and 81 are rejected under 35 U.S.C. §103 over Pourmand in view of Meyer (Nat. Prot., 2008, 3:267-78). The Office Action states that claims 68, 69, 74, 75, and 80-82 are rejected under 35 U.S.C. §103 over Pourmand in view of

Shoemaker (US 2008/0090239). Applicant submits that the claims are not obvious over any combination of those references.

In order to establish a prima facie case of obviousness, the prior art must provide motivation to modify a reference or to combine multiple references in a manner that would lead one of ordinary skill in the art to an applicant's claimed invention with a reasonable expectation of success. *See e.g., KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); and MPEP § 2143. Furthermore, an obviousness rejection cannot be established unless each claim element is disclosed in the cited art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Without a reference disclosing the missing claim elements, there can be no motivation of achieving the claimed invention or likelihood of success in doing so. *See Wyers v. Master Lock Co.*, 616 F.3d 1231 (Fed. Cir. 2010) (providing a prima face case requires a teaching or suggestion of all claim limitations along with an apparent reason to combine the references).

As discussed in the section above, Pourmand fails to disclose each and every claim element. Meyer and Shoemaker do not make up for the deficiencies of Pourmand.

Meyer merely reports a molecular barcoding method for sequencing multiple samples on the 454 platform. *See Meyer, Abstract.* Meyer does not disclose using MIPs to generate uniquely tagged target nucleic acid molecules. Shoemaker reports the use of nucleic acids from circulating tumor samples and fetal samples. *Shoemaker, paragraph [0004].* Shoemaker does not disclose or suggest applying a unique differentiator tag to each target nucleic acid to generate uniquely tagged molecules that can be used to identify amplicons. As with Pourmand, neither Meyer nor Shoemaker discloses the element of applying a unique differentiator tag to each independently isolated nucleic acid molecule to generate a plurality of uniquely tagged target nucleic acid molecules. Accordingly, no combination of those references makes the present claims obvious.

Applicant submits that the §103 rejection is overcome and should be withdrawn.

Double Patenting

Claims 68-70, 74, 75, and 79-82 are provisionally rejected on the ground of nonstatutory double patenting over claim 1 of co-pending Application No. 13/266,862 in view of Pourmand. Since the rejection is provisional, Applicant requests that it be held in abeyance.

Conclusion

If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: December 26, 2018

Respectfully submitted,
BROWN RUDNICK LLP

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63251303 v1

Petitioner Illumina, Inc., EX1003, p. 968

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	15231687	Filing Date	2016-08-08	Docket Number (if applicable)	MLB-002/04US 34468/10	Art Unit	1634
First Named Inventor	Gregory Porreca			Examiner Name	S. C. Pohnert		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☒ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 50-0369

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

X Patent Practitioner Signature

Applicant Signature

EFS - Web 2.1.16

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2018-12-26
Name	Thomas C. Meyers	Registration Number	36989
Applicant 2		Remove	
Signature		Date (YYYY-MM-DD)	
Name			

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal	
Application Number:	15231687
Filing Date:	08-Aug-2016
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/04US 34468/10
Filed as Small Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	950	950
		Total in USD ($)		**950**

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/231,687	08/08/2016	1634	800	MLB-002/04US 34468/10	11	1

CONFIRMATION NO. 6709

REPLACEMENT FILING RECEIPT

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

OC000000104736895

Date Mailed: 12/28/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Gregory Porreca, Cambridge, MA;
Uri Laserson, Boston, MA;

Applicant(s)

Molecular Loop Biosolutions, LLC, Cambridge, MA;

Power of Attorney: The patent practitioners associated with Customer Number 21710

Domestic Priority data as claimed by applicant

This application is a CON of 13/266,862 03/13/2012
which is a 371 of PCT/US10/01293 04/30/2010
which claims benefit of 61/182,089 05/28/2009
and claims benefit of 61/179,358 05/18/2009
and claims benefit of 61/178,923 05/15/2009
and claims benefit of 61/174,470 04/30/2009

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Petitioner Illumina, Inc., EX1003, p. 974

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/18/2016
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/231,687**
Projected Publication Date: Request for Non-Publication Acknowledged
Non-Publication Request: Yes
**********WARNING**********
Applicant has requested non-publication, certifying that the invention disclosed in this application has not been and will not be the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing; **and has also claimed** the benefit of an application filed in another country or under a multilateral agreement. Because the non-publication request and corresponding certification appears to be inconsistent with the priority claim, applicant is reminded that he/she has an obligation to promptly notify the Office and **rescind the non-publication request** if the invention disclosed in this application is the subject of an application filed in another country, or under a multilateral agreement, that requires eighteen-month publication.
**********WARNING**********
Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Petitioner Illumina, Inc., EX1003, p. 975

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Petitioner Illumina, Inc., EX1003, p. 976

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Petitioner Illumina, Inc., EX1003, p. 977

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10

CONFIRMATION NO. 6709

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

POA ACCEPTANCE LETTER

OC000000104736850

Date Mailed: 12/28/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/21/2018.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/dgela/

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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 05/08/2019

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
05/08/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Applicant-Initiated Interview Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA (FITF) Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) STEVEN C. POHNERT PhD. (3) _____.

(2) Annie Kock. (4) _____.

Date of Interview: 02 May 2019.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☑Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 68.

Identification of prior art discussed: none.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The representative contacted the examiner to obtain the status of the application. The examiner noted the RCE in the application had been processed. The examiner further noted the instant application was not one of the applications indicated by the office to be at the top of the examiners list. The examiner noted it would probably be at least a couple months before he would work on the application. No discussion of patentability occurred..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

	/Steven Pohnert/ Primary Examiner, Art Unit 1634

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 07/17/2019

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
07/17/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Office Action Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 12/26/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 68-78 and 80-82 is/are pending in the application.

5a) Of the above claim(s) 71-73 and 76-78 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68-70,74-75 and 80-82 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 10/21/2016 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Petitioner Illumina, Inc., EX1003, p. 983

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/26/2018 has been entered.

Claim Status and Formal matters

This action is in response to papers filed 12/26/2018.

Claims 68 has been amended.

Applicant's election without traverse of group I, claims 68-70, 74-75, 80-82 in the reply filed on 3/31/2017 is acknowledged.

Claims 71-73, 76-78 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/31/2017.

Claim 79 has been canceled.

Priority

2. The instant application was filed 08/08/2016 is a continuation of 13266862, filed 03/13/2012 and is a national stage entry of PCT/US10/01293 , International Filing Date: 04/30/2010, claims priority from provisional application 61182089, claims priority from provisional application 61179358, filed 05/18/2009, claims priority from provisional application 61178923, filed 05/15/2009, and priority from provisional application 61174470, filed 04/30/2009.

Claim Rejections - 35 USC § 102

3. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

4. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim(s) 68-69, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10)..

With regards to claim 68, Pourmand teaches

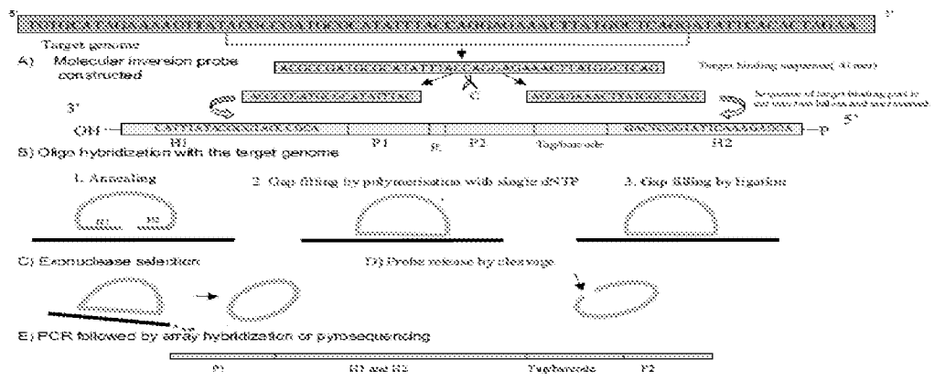

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each

target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Response to Arguments

The response traverses the rejection asserting, "The response traverses the rejection asserting, "amended claim 68 recites tagging each independently isolated target nucleic acid molecule of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag. For instance, the individual target nucleic acid molecules in the present invention may have been isolated in a reaction or vessel, but each molecule is tagged with a different, unique differentiator tag. The resulting molecules are amplified to generate amplicons that contain the uniquely tagged target nucleic acid molecules. Those amplicons are sequenced, and each

unique differentiator tag is sequenced along with the target nucleic acid molecule. " This argument has been thoroughly reviewed but is not considered persuasive as Poumard teaches in figure 2 that target sequences are tagged with unique barcodes via molecular inversion, the sequences are amplified including the tag and sequenced ((figure 1).

The response further asserts, "the present invention allows the starting molecules to be distinguished from each other to overcome bias associated with systematic and random errors in genome capture, amplification, and sequencing. See application as-filed, page 8. By providing unique differentiator tags for each target nucleic acid that follow the target through the amplifying and sequencing steps, the invention allows each starting target nucleic acid to be identified.." This argument has been thoroughly reviewed but is not considered persuasive as the response is providing arguments to limitations that are not in the claim. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further the unique barcodes of Pourmand can be used for this function.

The response concludes by asserting, "Pourmand does not disclose tagging each independently isolated target nucleic acid molecule of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag.." This argument has been thoroughly reviewed but is not considered persuasive as Pourmand teaches," A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A,

G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Thus Pourmand does disclose tagging each independently isolated target nucleic acid molecule of a plurality of target nucleic acid molecules obtained from a biological sample with a unique differentiator tag.

Thus the rejection is maintained.

6. Claim(s) 68-69, 75 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ronaghi (US PGPUB 2006/0008824) .

With regards to claim 68, Ronaghi teaches in claim 10 a method of labeling a nucleic acid by use of a unique primer and amplifying. Ronaghi teaches the amplified sequence can be sequenced (claim 10).

Ronaghi teaches, "the unique primer is attached to the nucleic acid molecule by ligating the adapter comprising a unique barcode to the nucleic acid molecule. In further embodiments, the unique barcode comprises a unique sequence of five nucleotides" (007).

Thus Ronaghi teaches a method of labeling target nucleic acids with a unique primer (or barcode), amplifying and sequencing the amplified sequence, thus identifying the sequence.

With regards to claim 69, Ronaghi teaches sequencing the amplified sequence which would identify the unique differentiator tag.

With regards to claim 75, Ronaghi teaches, "In certain embodiments, the source of nucleic acid is selected from the group consisting of: a BAC clone, a bacterium, and a tissue sample.

Response to Arguments

This is a new ground of rejection.

Claim Rejections - 35 USC § 103

7. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

8. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 68-70, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Meyer (Nature Protocols (2008) volume 3, pages 267-278, epublished Jan 31, 2008).

With regards to claim 68, Pourmand teaches

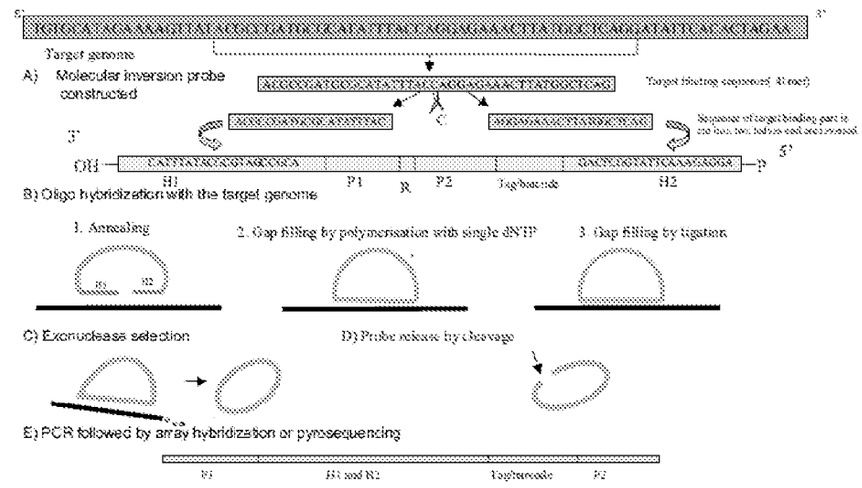

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV).

These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach determining presence of sequencing or amplification errors.

However, Meyer teaches preparing batches of barcoded nucleic acids (unique tags) by attaching barcodes or sequence tags to nucleic acids. See p. 271, Box 1; Quality control and Procedure. The barcodes are added to purified PCR products or positive control PCR products (p. 272, Reagent Setup; p. 273, step 10). The batches are pooled and sequenced in parallel. A contamination in a batch of barcodes is

determined by determining a frequency at which cross-contamination of adapters occurred during synthesis or dilution. Meyer further teaches a formula that takes into account and estimates false assignment that occurs due to sequencing errors and cross-contamination of barcoding adapters during synthesis and dilution (Box 1). Therefore, Meyer teaches identifying a contamination in a batch of barcodes (unique tags)by determining a frequency at which an incorrect adapter sequence occurs in the batches.

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis. .

Response to Arguments

The response traverses by asserting the teachings of the Pourmand does not teach all the limitations of the independent claim. This argument has been thoroughly reviewed but is not considered persuasive for the reasons of record.

10. Claim 68-69, 74-75, 80-82 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Shoemaker (US20080090239 published 4/17/2008).

With regards to claim 68, Pourmand teaches

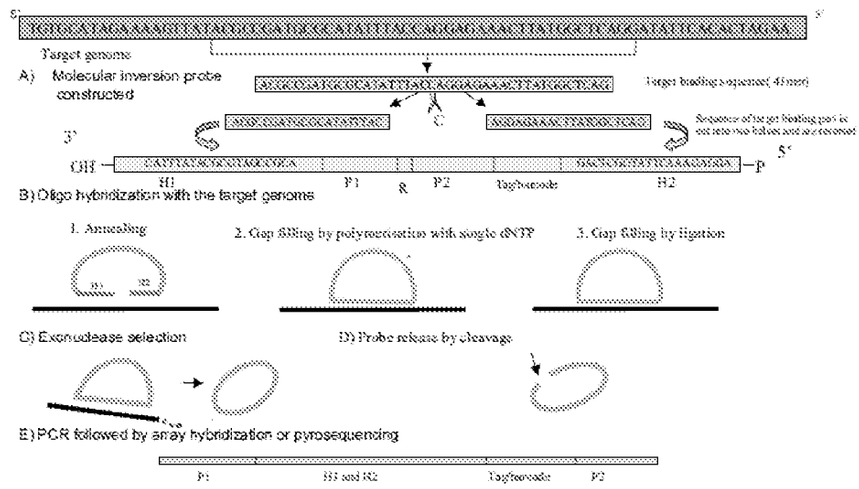

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV).

These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach use of nucleic acids from circulating tumors or fetal nucleic acids.

However, Shoemaker teaches, "[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large

number of maternal cells in the blood which make the analysis time consuming and prone to error."

Shoemaker teaches, "0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying, quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc."

Shoemaker teaches, "In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods, which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detecting circulating tumor nucleic acids or circulating fetal nucleic acids in the method of Poumard. The artisan would be motivated to use methods that are less invasive methods than aminocentesis or tumor biopsy. The artisan would have a reasonable expectation of success as the artisan is merely using known samples in known methods.

Response to Arguments

The response traverses by asserting the teachings of the Pourmand does not teach all the limitations of the independent claim. This argument has been thoroughly reviewed but is not considered persuasive for the reasons of record.

11. Claim 68-69, 74-75, 80-82 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Ronaghi (US PGPUB 2006/0008824) and Shoemaker (US20080090239 published 4/17/2008).

Ronaghi does not specifically teach use of nucleic acids from blood sample, circulating tumors or fetal nucleic acids. Rongahi does not specifically teach determining copy number.

However, Shoemaker teaches, "[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large number of maternal cells in the blood which make the analysis time consuming and prone to error."

Shoemaker teaches, "0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying, quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc."

Shoemaker teaches, "In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods, which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes."

Shoemaker teaches, "In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the

fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes" (0010)

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detecting copy number in circulating tumor nucleic acids or circulating fetal nucleic acids in the method of Ronaghi. The artisan would be motivated to use methods that are less invasive methods than aminocentesis or tumor biopsy to determinecopy number.. The artisan would have a reasonable expectation of success as the artisan is merely using known samples in known methods.

Response to Arguments

This is a new ground of rejection.

12. Claim 68-70, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over by Ronaghi (US PGPUB 2006/0008824) and Meyer (Nature Protocols (2008) volume 3, pages 267-278, epublished Jan 31, 2008).

With regards to claim 68, Ronaghi teaches in claim 10 a method of labeling a nucleic acid by use of a unique primer and amplifying. Ronaghi teaches the amplified sequence can be sequenced (claim 10).

Ronaghi teaches, "the unique primer is attached to the nucleic acid molecule by ligating the adapter comprising a unique barcode to the nucleic acid molecule. In further embodiments, the unique barcode comprises a unique sequence of five nucleotides" (007).

Thus Ronaghi teaches a method of labeling target nucleic acids with a unique primer (or barcode), amplifying and sequencing the amplified sequence, thus identifying the sequence.

With regards to claim 69, Ronaghi teaches sequencing the amplified sequence which would identify the unique differentiator tag.

With regards to claim 75, Ronaghi teaches, "In certain embodiments, the source of nucleic acid is selected from the group consisting of: a BAC clone, a bacterium, and a tissue sample.

Ronaghi does not specifically teach determining presence of sequencing or amplification errors.

However, Meyer teaches preparing batches of barcoded nucleic acids (unique tags) by attaching barcodes or sequence tags to nucleic acids. See p. 271, Box 1; Quality control and Procedure. The barcodes are added to purified PCR products or positive control PCR products (p. 272, Reagent Setup; p. 273, step 10). The batches are pooled and sequenced in parallel. A contamination in a batch of barcodes is determined by determining a frequency at which cross-contamination of adapters occurred during synthesis or dilution. Meyer further teaches a formula that takes into account and estimates false assignment that occurs due to sequencing errors and cross-contamination of barcoding adapters during synthesis and dilution (Box 1). Therefore, Meyer teaches identifying a contamination in a batch of barcodes (unique tags)by determining a frequency at which an incorrect adapter sequence occurs in the batches.

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis. .

Response to Arguments

This is a new ground of rejection.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory

double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

14. Claims 68-70, 74-75, 79-82 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 13/266,862 in view of Pourmand (BMC informatics (2006) volume 7:500, pages 1-10). This is a provisional nonstatutory double patenting rejection.

Claim 1 of ‘862 is drawn to A method for analyzing a target nucleic acid, the method comprising: providing a sample comprising a target nucleic acid, contacting the sample with a probe set to generate hybridized probes, the probe set comprising a

plurality of different molecular inversion probes (MIPs), each MIP comprising a 5' targeting arm, a central region, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the target nucleic acid, wherein the probe set has a staggered layout such that all of the MIPs capture the target, and some MIPs in the probe set capture additional flanking sequence; converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target nucleic acid; isolating the plurality of circularized probes; and acid sequences of different subregions; and analyzing the isolated subregions.

Claims of '862 do not specifically teach amplifying or a unique barcode.

However, Pourmand teaches

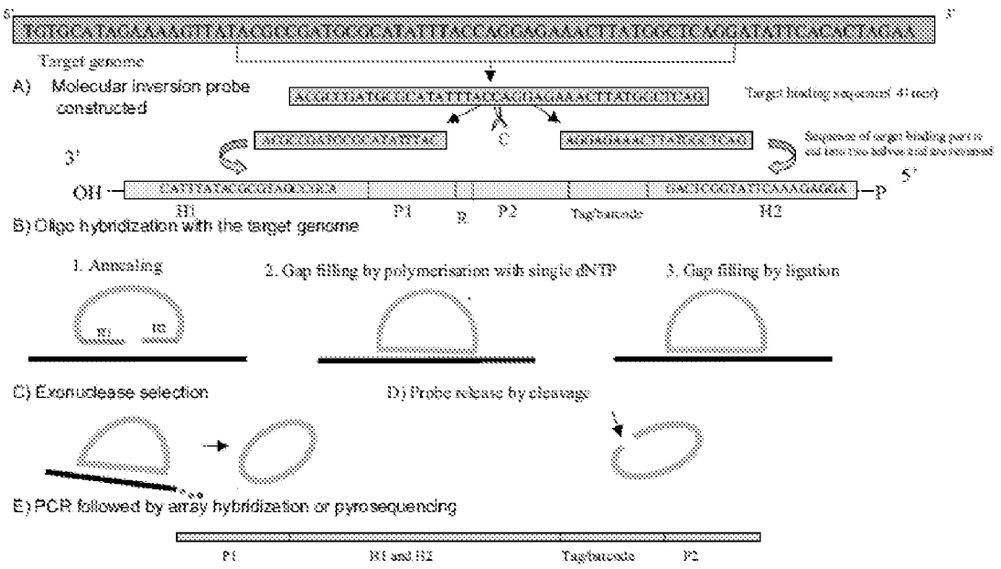

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common

middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column).

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the moleucles, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical

tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Other dependent claims are obvious variants of the methods of Pourmand and '862.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to improve the molecular inversion probe method of '862 with unique differentiator tags with amplifying and sequencing of Poumard. The artisan would be motivated to amplify and sequence the molecular inversion probes to increase the amount of nucleic acid being detected and thus increase the sensitivity by an art . The artisan would have a reasonable expectation of success as the artisan is merely be using art accepted methods of analysis of nucleic acid sequences using molecular inversion probes.

Response to Arguments

The response request the ODP rejection be held in abeyance. Thus the rejection is maintained.

Summary

No claims are allowed.

Kincaid (USPGPUB 2006/0263789) and Akhras (PLOS one (2007) volume 9, e915, pages 1-6) at a reference that may be of interest.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C POHNERT PhD whose telephone number is (571)272-3803. The examiner can normally be reached on Monday- Friday about 6:00 AM-5:30 PM, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven Pohnert/
Primary Examiner, Art Unit 1634

Notice of References Cited	Application/Control No. 15/231,687	Applicant(s)/Patent Under Reexamination Porreca et al.	
	Examiner STEVEN C POHNERT PhD	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20060008824-A1	01-2006	Ronaghi; Mostafa	C12Q1/6874	435/6.14
*	B	US-20060263789-A1	11-2006	Kincaid; Robert	C12Q1/68	435/6.12
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Akhras (PLOS one (2007) volume 9, e915, pages 1-6)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Petitioner Illumina, Inc., EX1003, p. 1007

Electronic Acknowledgement Receipt	
EFS ID:	37546849
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Sandra Richards
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	24-OCT-2019
Filing Date:	08-AUG-2016
Time Stamp:	12:01:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$120
RAM confirmation Number	E20190NC01162733
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	34468_30US_-_WO2007061284A1.pdf	1193373 75b6280e3fad2a783631375d7abc1bfae9059ae8	no	76
Warnings:					
Information:					
2	Foreign Reference	WO2011066476A1.pdf	5302814 286fa76cdf2faf9bc9484b68be087b8ea451f1d8	no	77
Warnings:					
Information:					
3	Foreign Reference	WO2011067378A1.pdf	1915901 60c3eb2dd2e67ad5b7b27d785d2de9266ff89578	no	36
Warnings:					
Information:					
4	Non Patent Literature	34468_8US_-_Akhras-2007-PLoSOne.PDF	212811 290afe15df59bce64f053e8d4059d06bb72159c8	no	6
Warnings:					
Information:					
5	Non Patent Literature	Li-2003-EMBOJ.pdf	560612 9f67fffae4b8643ec7174a7d2ddbfc3d0849d6be	no	12
Warnings:					
Information:					
6	Non Patent Literature	34468_30US_-_Wahl-1979-PNAS.pdf	1446306 1948e732454e8e31fe6988253942fd1402931777	no	5
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7	Information Disclosure Statement (IDS) Form (SB08)	34468_10US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1035524 fb2f5aca0dbf1f93fff8a3d87353a8f356ee4d6f	no	6
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Information:					
8	Non Patent Literature	34468_8US-Meyer-2008-NatProt.pdf	1111788 26640678868449adb3218c78f1ebc9e169e8cf2b	no	12
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Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	30408 90329e2e6266c6253ca041462bbf54deeafd32a1	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	12809537	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/04US 34468/10

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2019-10-24
Name/Print	Thomas C. Meyers	Registration Number	36,989

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/04US 34468/10

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	2	9115387		2015-08-25	Umbarger	
	3	9677124		2017-06-13	Umbarger	
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	2	20060008824	A1	2006-01-12	Ronaghi et al.	

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	Attorney Docket Number	MLB-002/04US 34468/10

	3	20060263789	A1	2006-11-23	Kincaid	
	4	20100216153	A1	2010-08-26	LAPIDUS et al.	
	5	20110288780	A1	2011-11-24	Rabinowitz et al.	
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	8	20130130921	A1	2013-05-23	Gao et al.	
	9	20140228226	A1	2014-08-14	Yin et al.	
	10	20140342354	A1	2014-11-20	Evans et al.	
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	1	2007/061284	WO	A1	2007-05-31	Plant Res Int BV		
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	1	Akhras, 2007, Connector inversion probe technology: A powerful one-primer multiplex DNA amplification system for numerous scientific applications, PLoSOne 9:e915	
	2	Li, 2003, DNA binding and cleavage by the periplasmic nuclease Vvn: a novel structure with a known active site, EMBO J 22(15):4014-4025	
	3	Meyer, 2008, Parallel tagged sequencing on the 454 platform, Nat Protocol 3(2):267-278	
	4	Wahl, 1979, Efficient transfer of large DNA fragments from agarose gels to diazobenzyloxymethyl-paper and rapid hybridization by using dextran sulfate, PNAS 76:3683-3687	

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Application Number:	15231687
Filing Date:	08-Aug-2016
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Sandra Richards
Attorney Docket Number:	MLB-002/04US 34468/10
Filed as Small Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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EFS ID:	37551833
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
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1		MLB-002-04US_Response_10-24-19.pdf	43061 74935560ef3640c6779bb1e3626d12278df15ab7	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	10	
Warnings:					
Information:					
2	Miscellaneous Incoming Letter	PourmandAnnotated.pdf	7541365 78329ca3b3ffc3988cb8320e98384403a9ace9e4	no	80
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30792 7162153086b0e713f70f1ee5c17ec3adc71e655f	no	2
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Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

This paper is in response to a non-final Office Action mailed July 17, 2019 from the United States Patent and Trademark Office. Applicant petitions for a one-month extension of time, thereby extending the period for response up to, and including, November 17, 2019.

The fees for a one-month extension of time are submitted herewith. Applicant believes no additional fees are due with this paper. Nevertheless, Applicant authorizes any and all required fees due with this response to be charged to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 5.

AMENDMENTS TO THE CLAIMS

Please amend the claims as follows. The following listing of claims will replace all prior versions of claims in the application.

1-67. (Canceled)

68. (Currently Amended) A method for nucleic acid identification, the method comprising the steps of:

obtaining a biological sample comprising a plurality of target nucleic acid molecules;

tagging each ~~independently isolated~~ target nucleic acid molecule ~~of a plurality of target nucleic acid molecules obtained~~ from [[a]]the biological sample with one or more of a plurality of random locus-independent ~~unique~~ differentiator [[tag]]tags, thereby generating ~~to generate~~ a plurality of ~~uniquely~~ tagged target nucleic acid molecules, the differentiator tags remaining attached to the target nucleic acid molecules through amplification and sequencing steps to allow unique identification of each target nucleic acid molecule;

amplifying said uniquely tagged target nucleic acid molecules to generate amplicons that contain the uniquely tagged target nucleic acid molecules;

identifying the target nucleic acid molecule by sequencing the amplicons obtained in said amplifying step, wherein each ~~unique~~ differentiator tag is sequenced along with the target nucleic acid molecule to allow each sequencing read to be linked to the target molecule from which it was derived~~; and~~

~~identifying a sequence for said nucleic acid molecules~~.

69. (Currently Amended) The method of claim 68, wherein said identifying step comprises identifying said ~~unique~~ differentiator tags.

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70. (Previously Presented) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon the number of said unique differentiator tags.

71. (Withdrawn) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

72. (Withdrawn) The method of claim 71, wherein said common identifier is used to identify a sample source.

73. (Withdrawn) The method of claim 72, wherein said common identifier is used to identify a patient.

74. (Previously Presented) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (Previously Presented) The method of claim 68, wherein said plurality of nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (Withdrawn) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

77. (Withdrawn) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

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78. (Withdrawn) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

79. (Canceled)

80. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are circulating tumor nucleic acid molecules.

81. (Previously Presented) The method of claim 68, further comprising the step of determining the copy number of a genomic region or transcript in a patient from whom the sample is obtained.

82. (Previously Presented) The method of claim 68, wherein said nucleic acid molecules are maternally-circulating fetal or placental nucleic acid molecules.

83. (New) The method of claim 68, wherein a same set of differentiator tags is used across multiple loci.

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REMARKS

Claims 68-78 and 80-83 are pending in the application. Claims 68 and 69 are currently amended, and claim 83 is newly added. Claims 1-67 and 79 were previously canceled. Claims 71-73 and 76-78 were previously withdrawn.

Support for the claim amendments and new claim is found throughout the as-filed application. In particular, the feature "plurality of random locus-independent differentiator tags" in amended claim 68 is supported at lines 6-20 of page 39, lines 21-32 of page 40, lines 10-22 of page 41, and Examples 4-7. The feature "the differentiator tags remaining attached to the target nucleic acid molecules through amplification and sequencing steps to allow unique identification of each target nucleic acid molecule" in amended claim 68 is supported at lines 13-33 of page 6, line 21 of page 39 to line 20 of page 40, lines 3-9 of page 41, and Examples 6-7. The feature "identifying the target nucleic acid molecule by sequencing the amplicons obtained in said amplifying step, wherein each differentiator tag is sequenced along with the target nucleic acid molecule to allow each sequencing read to be linked to the target molecule from which it was derived" in amended claim 68 is supported at lines 13-33 of page 6, line 21 of page 39 to line 20 page 40, lines 3-33 of page 41, lines 1-12 of page 42, and Examples 6-7. The new claim 83 feature is supported at least at lines 24-26 of page 19.

No new matter is added.

Examiner Interview

Applicant and the undersigned representative thank the Examiner for his time and consideration in conducting the video interview on October 22, 2019 with inventor Dr. Gregory Porreca and representatives for the Applicant. The Pourmand (BMC Informatics, 2006, 7:500) and Ronaghi (US 2006/0008824) references were discussed in the interview, along with proposed claim amendments. Applicant submits this response in furtherance of those discussions.

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Rejections under 35 U.S.C. §102

The Office Action, at page 3, states that claims 68, 69, 74, 75, and 81 are rejected under 35 U.S.C. §102(b) over Pourmand. The Office Action, at page 7, states that claims 68, 69, and 75 are rejected under 35 U.S.C. §102(b) over Ronaghi.

Applicant respectfully submits that Pourmand and Ronaghi do not anticipate the present claims because neither reference discloses every element of the amended claims.

The invention provides methods to identifying target nucleic acid molecules. As recited in amended claim 68, each nucleic acid molecule in a sample is tagged with one or more of a plurality of random locus-independent differentiator tags. The tags remain with the starting molecules through amplification and sequencing steps. The tags allow the resulting sequences to be traced back to the original starting molecule from which the sequence was derived. Thus, the present invention allows identification of starting target molecules within the sample by providing differentiator tags for each target nucleic acid that follow the target through the amplifying and sequencing steps.

By allowing the starting molecules to be distinguished from each other, the invention provides methods that overcome bias or error associated with systematic and random errors in genome capture, amplification, and sequencing. In particular, the invention allows for a reduction in errors associated with the capture and amplification of nucleic acids. *See as-filed specification, lines 13-33 of page 6, lines 1-4 of page 7, lines 1-7 of page 28, and lines 25-28 of page 38.*

Pourmand is directed to locus detection. MIPs are used as a detection assay to detect the presence or absence of loci. There is one tag per locus, and the tags are used to track the locus. The barcode identifies the specific gene, as stated in Pourmand at page 2, bottom of the first column. Furthermore, the examples provided by Pourmand confirm that there is one tag/barcode for each genome included in the assay. That is, all candidate probes have the same tag sequence

for a given locus or genome and each locus or genome has a different and distinct tag. *See annotated supplementary material of Pourmand provided herewith (see annotations at pages 14, 16, 30, 31, 38, 39, 47, 48, 53, 59, 60, 71, and 80).*

In contrast to Pourmand, tags in the present invention are used to track target molecules in the starting sample and are locus-independent (i.e., each locus may have multiple different tags associated with it). Moreover, tags used in the invention can be randomers. *See as-filed specification, lines 10-22 of page 41.* This means that the random, locus-independent tags of the invention are useless for locus identification because they cannot be uniquely associated with a locus (i.e., they identify multiple loci). Therefore, it is clear that the use of tags as taught by the present claims would render Pourmand inoperative because the tags could not possibly distinguish the presence or absence of a locus.

Ronaghi is directed to sequence assembly using BACs. Ronaghi reports tags to identify the BAC clone from which a sequence was obtained in order to aid sequence assembly of adjacent fragments in the genome. Ronaghi uses a unique pentamer to identify all the clones from a given BAC. *See Ronaghi, paragraphs [0015] and [0058]* (reporting fragmenting a BAC library and saturating the fragments with a unique barcode, which will later identify the BAC from which the fragments were obtained). To achieve the purpose of Ronaghi, an independent set of tags is needed to identify each BAC. The tags in Ronaghi are used to identify the BAC and not the original starting target. Applying the present claims (in which tags identify a specific molecule regardless of its source) to Ronaghi's sequence assembly disclosure would result in amplified sequence that could not be traced back to the clonal library from which they were generated, thus frustrating the entire purpose of the Ronaghi report.

Applicant submits that neither Pourmand nor Ronaghi anticipate independent claim 68. Neither reference discloses using locus-independent differentiator tags that remain attached through amplification and sequencing steps to allow a resulting sequence to be traced back to the original starting target molecule from which the sequence was derived. Thus, the invention

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provides for identification of each target nucleic acid molecule from the starting sample after amplification and sequencing. Dependent claims 69, 74, 75, and 81 are not anticipated for at least the same reasons as claim 68. Accordingly, the §102 rejections are overcome.

Rejections under 35 U.S.C. §103

The Office Action, at page 8, states that claims 68-70, 74, 75, and 81 are rejected under 35 U.S.C. §103 over Pourmand in view of Meyer (Nat. Prot., 2008, 3:267-78). The Office Action, at page 11, states that claims 68, 69, 74, 75, and 80-82 are rejected under 35 U.S.C. §103 over Pourmand in view of Shoemaker (US 2008/0090239). The Office Action, at page 15, states that claims 68, 69, 74, 75, and 80-82 are rejected under 35 U.S.C. §103 over Ronaghi in view of Shoemaker. The Office Action, at page 17, states that claims 68-70, 74, 75, and 81 are rejected under 35 U.S.C. §103 over Ronaghi in view of Meyer.

Applicant submits that the claims are not obvious in view of the cited references.

In order to establish a *prima facie* case of obviousness, three basic criteria must be established by the Patent Office. First, there must be a suggestion in the cited art to modify a reference or to combine multiple references in a manner that would lead one of ordinary skill in the art to an applicant's claimed invention. Second, the cited references themselves must convey a reasonable expectation of success in arriving at the claimed invention based upon the proposed modification or combination. Finally, the teaching or suggestion to make the claimed invention must be found in the prior art and not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). For a claim to be obvious over a combination of references, there must be some articulated reason with some rationale underpinning for why one of skill in the art would have made the proposed combination. *KSR v. Teleflex*, 550 U.S. at 418 (2007).

As discussed above, Pourmand and Ronaghi fail to disclose each and every claim element. Meyer and Shoemaker do not make up for the deficiencies of Pourmand and Ronaghi.

Meyer reports a molecular barcoding method for sequencing multiple samples on the 454 platform. *Meyer, Abstract*. Meyer does not disclose using locus-independent differentiator tags to identify starting target nucleic acid molecules. Shoemaker reports the use of nucleic acids from circulating tumor samples and fetal samples. *Shoemaker, paragraph [0004]*. Shoemaker does not disclose applying locus-independent differentiator tags that remain attached through amplification and sequencing steps to allow identification of sequences to be traced back to the starting target nucleic acid from which the sequence was derived. Therefore, neither Meyer nor Shoemaker remedies the deficiencies of Pourmand and Ronaghi. Accordingly, no combination of those references makes the present claims obvious.

Applicant submits that the §103 rejections are overcome and respectfully requests withdrawal of the rejections.

Double Patenting

Claims 68-70, 74, 75, and 79-82 are provisionally rejected on the ground of nonstatutory double patenting over claim 1 of co-pending Application No. 13/266,862 in view of Pourmand.

Since the rejection is provisional, Applicant requests that it be held in abeyance.

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CONCLUSION

If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: October 24, 2019

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PathogenMIPer: a tool for the design of molecular inversion probes to detect multiple pathogens

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Abstract

Background: Here we describe PathogenMIPer, a software program for designing molecular inversion probe (MIP) oligonucleotides for use in pathogen identification and detection. The software designs unique and specific oligonucleotide probes targeting microbial or other genomes. The tool tailors all probe sequence components (including target-specific sequences, barcode sequences, universal primers and restriction sites) and combines these components into ready-to-order probes for use in a MIP assay. The system can harness the genetic variability available in an entire genome in designing specific probes for the detection of multiple co-infections in a single tube using a MIP assay.

Results: PathogenMIPer can accept sequence data in FASTA file format, and other parameter inputs from the user through a graphical user interface. It can design MIPs not only for pathogens, but for any genome for use in parallel genomic analyses. The software was validated experimentally by applying it to the detection of human papilloma virus (HPV) as a model system, which is associated with various human malignancies including cervical and skin cancers. Initial tests of laboratory samples using the MIPs developed by the PathogenMIPer to recognize 24 different types of HPVs gave very promising results, detecting even a small viral load of single as well as multiple infections (*Akhras* et al, personal communication).

Conclusion: PathogenMIPer is a software for designing molecular inversion probes for detection of multiple target DNAs in a sample using MIP assays. It enables broader use of MIP technology in the detection through genotyping of pathogens that are complex, difficult-to-amplify, or present in multiple subtypes in a sample.

Background

Detection of the different types and subtypes of a pathogen is very important in clinical diagnosis. Over the past several years, the development and application of molecular diagnostic techniques has initiated a revolution in the diagnosis and monitoring of infectious diseases. Advances in molecular and cell biology have provided us with an understanding of the mechanisms of disease at the molecular level that can now be translated into designing new diagnostic, prognostic, and therapeutic tools. It is now

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possible to genotype/subtype pathogens to increase the accuracy and reproducibility of diagnosis. Detection of microbial DNA can provide not only a signature for the presence of a disease, but may also indicate a drug-resistant genotype, a particularly virulent subtype, a subtype associated with other clinically important sequelae, or the presence of multiple subtypes. These advances should open the way for administering more effective and efficient treatment for the control, prevention and cure of diseases. There are several multiplex detection methods currently in use, like DNA microarray, MUCH-AMASE, multiple sequencing and pyrosequencing [1-5], but they perform poorly in subtyping of pathogens in a sample, as all of them needs a pre-amplification of DNA through a PCR, and thus target a region of the whole genome where PCR primers are possible. This limits the number of target organisms or types/subtypes that can be detected in an assay. Genomes of some viral pathogens are too diverse to design a PCR primer pair whereas some pathogen genomes have types and subtypes with less diversity for designing specific probes.

Molecular Inversion Probe (MIP) technology was initially developed for the detection of single nucleotide polymorphisms (SNPs) in human genes [6,18]. MIP technology has been shown to work well for multiplexing, i.e. massive parallel processing (12,000 MIPs in the same reaction tube) [7]. The power and versatility of MIP technology makes it perfectly suited for the identification and quantification of microbes. MIP's high sensitivity and specificity in detecting large numbers of SNPs [6,7] should allow one to harness this technology to detect a large number of pathogens and to identify multiple infections in an individual sample. MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube.

A molecular inversion probe is comprised of genomic recognition sequences, common amplification sequences and a molecular barcode for each genotype assigned to a specific gene. This probe is a linear oligonucleotide with target-complementary sequences at the ends and a non-complementary linking segment in between (Figure 1A). Upon hybridization, the ends are brought together, creating a double helix with a gap of one or more nucleotides such that polymerization to fill the gap and subsequent ligation will occur only in the presence of a specific nucleotide. Upon appropriate filling and ligation, the oligonucleotide is circularized and, due to the helical nature of double-stranded DNA, it encircles the target DNA strand (Figure 1B). Probes that are successfully filled and ligated are amplified using universal primers (Figure 1C–E). A universal barcode sequence allows for array detection and quantification of amplified probe. This strategy provides the following advantages: i) high level accuracy is reliably obtained based on fidelity of both polymerase and ligase in the gap-fill step, ii) high specificity is ensured from hybridization, polymerization and ligation; indeed these latter enzymatic reactions together result in very specific and accurate pathogen typing. The use of a MIP in genomic detection techniques is shown in figures 1A–1E.

In order to target the entire genome of a pathogen, the probes must be very sensitive, and long enough to detect even a few copies of the pathogen DNA in the sample. The reliability of the MIP assay depends wholly on the specificity and binding efficiency of the probes. To harness MIP technology and make it available for widespread clinical use, it will be necessary for researchers to rapidly design high quality probes. The classical approach for designing oligonucleotides, that is found in existing softwares [20-24] were mainly developed for the design of microarray probes, PCR or sequencing primers. Most of these software tools use the same algorithms to design probes based on the criteria specified by the user, and these approaches are not always adapted to complex biological samples, for which multiple organism detection is needed. The available tools for MIP design [3,17] do not check for cross-hybridization with the potential background, or host genome. This is a critical factor in that cross-hybridization could lead to misinterpretation of the results in a clinical diagnosis. Here we describe PathogenMIPer, a tool for designing unique and specific probes targeting microbial (or other) genomes. In contrast to other MIP design programs, our system designs highly unique probes specific for each target sequence through multiple, successive steps of evaluation of candidates, followed by a final check against non-target genomes potentially present in the sample that could otherwise cause background noise or interfere with signal. Because of its reliability and ease of use, PathogenMIPer can be used by specialists and non-specialists alike, which would allow MIP technology to become more widely accessible.

Implementation

A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a unique tag which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. The total length of the MIP will be around 100 bases, depending on the lengths of target-binding homologues, primer sequence, restriction site and unique tag.

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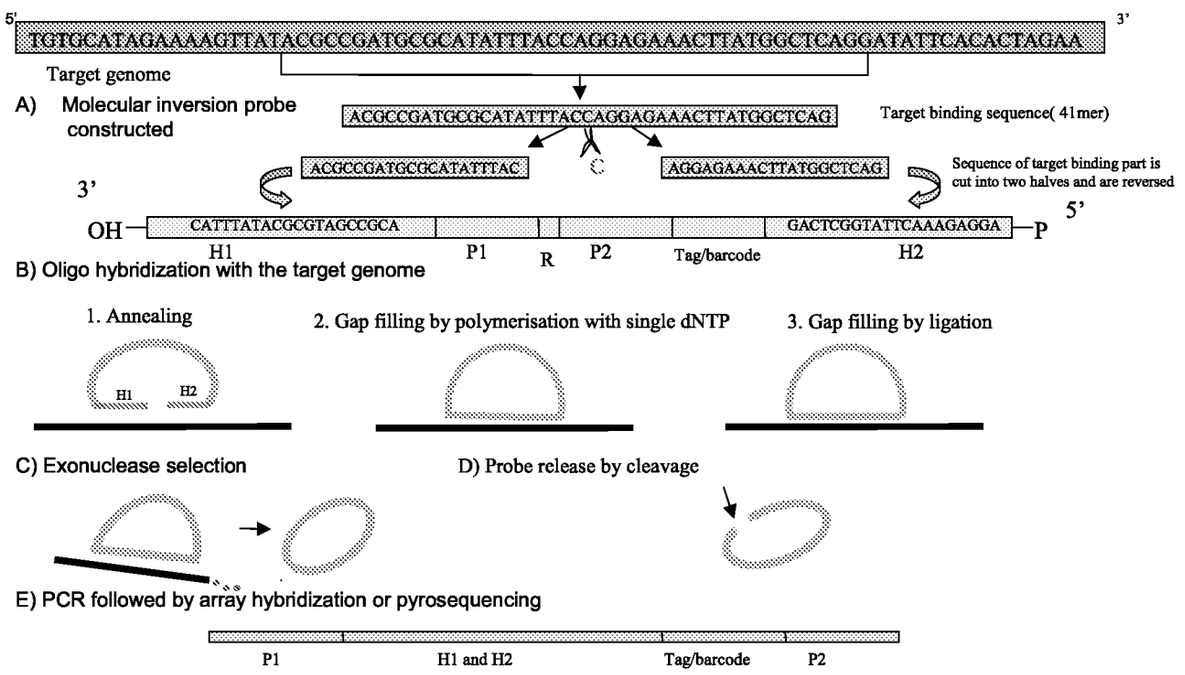

Figure 1

Steps involved in a standard MIP Assay (Steps A – E). H1 & H2 – Two segments homologous to the target genome, P1 & P2 – Two universal primers common for all MIPs, R – Cleavage site. A) A Molecular inversion probe constructed using PathogenMIPer software, for each of the organism to be detected in the MIP assay. An oligo of user specified length is extracted from the target genome, and cut into two halves, reversed and tailored with the primer and other tags. B) Oligo hybridization with the samples. Done enzymatically – a mixture of the genomic DNA, MIP probes specific for all the targets, a thermostable polymerase and ligase, is heat denatured and brought to annealing temperature. i) Two sequences targeting each terminus of the probe hybridize to complementary sites in the genome creating a circular conformation with a single nucleotide gap between the termini of the probe. All the MIP probes are designed to have the same nucleotide at this position. ii) Unlabeled dATP/dGTP/dCTP/dTTP (any one selected by the user while designing the probe) is added to the reaction and the polymerase adds the nucleotide to the gap, and then iii) the ligase closes the gap to form a circular molecule that encircles the genomic strand, to which it's hybridized. C) Exonucleases are added to remove the excess unreacted linear probes and any linear genomic DNA. The reactions are then heated to inactivate the exonucleases. D) The probes are released from the genomic DNA by reacting with uracil-N-glycosylase. E) PCR reagents are added along with the common PCR primer pair. The reactions are subjected to thermal cycling, with the result that only circularized probes which bound to the specific target, are amplified. The probes are detected using a tag microarray or pyrosequencing.

The software first generates target sequences and then in several consecutive steps eliminates unfit candidates. In order to minimize the time required to perform a design task, oligos are processed in several steps of increasing computational intensity, with a recursive elimination of unfit candidate probes at each of successive steps. The processing steps in our MIP design are as follows:

1. Candidate probes for each of the target sequences are generated with a userspecified binding length.

2. Candidates with a continuous stretch of six or more of the same base are eliminated.

3. The middle base is checked for the preferred base (A|G|T|C). Candidates without the preferred middle base are eliminated.

4. The remaining candidates are checked against non-target genomes. If an absolute match is found, the candidate is eliminated.

5. The middle 11-base region is checked against other genomes to ensure uniqueness of probes and specificity of the assay.

Automatically, the nonspecific candidates previously identified for other targets are also removed.

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6. Candidates are checked for their melting temperature (Tm) and those that are beyond the desired range are eliminated.

7. Candidate probes whose similarity to non-target sequences exceeds a userspecified maximum are removed.

8. The remaining probes are screened against the potential background caused by the host genome using an online BLAST search [8] of the probes against the genome of the host.

9. In the final step, the tags are added to complete the design of ready-to-order probes. The tags are checked against the binding segments of all probes, to make sure that the addition of tags does not create a new recognizable sequence that may produce noise, false positives, or background during target detection.

Initially (step 1), all sequences of the target with the specified binding length are considered as candidate probes. Each target-specific sequence is first examined for the presence of poly As, Cs, Gs or Ts and candidates with more than 6 repeats are eliminated (step 2). After completing the check of the middle base (step 3) and an initial search to eliminate homology with non-targets (step 4), the middle 11 base region of the probe, is checked against a non-target sequence (step 5) and those with a continuous stretch of similarity with the non-target sequences are eliminated (step 6). In step 7, the candidates are checked for their Tm using the nearest neighbor method [9-11]. Surviving candidates for each target are stored in a file for later sorting and validation.

Each target sequence will have a pool of anywhere from zero to a several thousands of probe candidates. The best of the unique candidates are selected from each pool by a selective filter tool (step 8). In step 8, each of the candidates is scored for number of matching bases with the non-target sequences using a BLAST search [8]. The scoring is done in such a way that higher scores are given for matches towards the middle region of the probe, where the probe initiates binding with the target. When a candidate has a number of matching bases greater than the cut-off value, that candidate is eliminated.

The design strategy used in our software evaluates specificity at each step. Many existing oligo design tools [12-16] are difficult to customize to attain the specificity required for a molecular inversion probe. The application that most closely addresses the needs of MIP design (ProbeMaker) [11] falls short when the goal is to design unique MIPs for distinguishing between 105 HPV types at the same time. In general, there are many tools that are useful for designing MIPs for the detection of SNPs [11], but they fail when challenged to design MIPs for many subtypes of a complex genome, such as MIPs to detect 105 HPV types concurrently. Even if the number of tests or restrictions on the probe candidates is reduced, these programs tend to return a number of probes that is equal to the number of all HPV types without any uniquely selective probes (in the sense having more than 90% match in a non-target HPV type). In addition to these problems, most of these probes have close matches in the host genome, a property that is critical to remove from a probe that will be used for the detection of multiple subtypes of pathogens.

In order to design a sensitive, reliable and consistent MIP assay, all probes for each target genome in the assay must be very selective and the selectivity determinants should be located mainly in the middle of the target binding region. These criteria are not enforced in any of the existing tools. The problem is made more complicated in a real biological situation, as some parts of the genome and of the target(s) may be highly mutated, so that even probes that are designed for a consensus target with high specificity may fail to bind to the actual targets, because of natural variation. Thus a pathogen MIP design strategy should include a user option to avoid particularly variable regions of the genome during the design of target-specific probes. The PathogenMIPer software allows for such options.

PathogenMIPer designs candidate probes for each target sequence through several computational steps as is shown in Figure 2. The PathogenMIPer software accepts sequence data, criteria for probe design, tags and primer sequences through a graphical user interface. After the data are validated and carefully checked, a summary view of the design is displayed and confirmed by the user to actually start a design process. The criteria that are put in by the user and accepted by the program are length of homologous sites, middle base identity, and Tm. A length in the range 40–60 is ideal for the length of homologous parts of the probe. This will give an ideal Tm of 50–60°C. The actual program runs in four stages on a PC and the results are written as a document file.

Laboratory validation of software results

We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common

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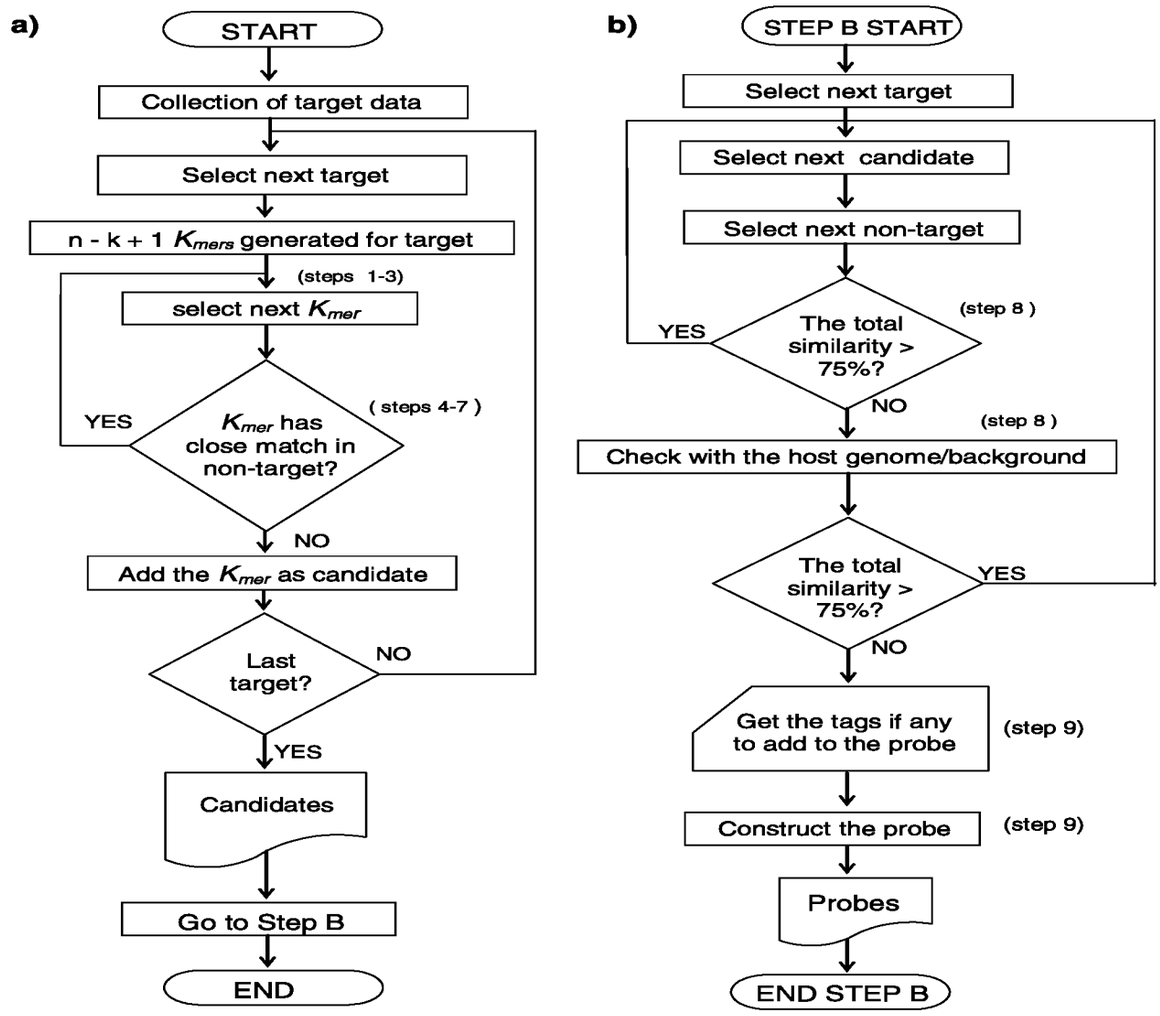

Figure 2
Steps in the design of MIPs: a) The software generates candidates for each target, based on the user specified criteria. b) The candidates are checked for their nonspecific binding with non targets and the host genome and nonspecific ones are eliminated and the specific ones are selected for designing MIP probes. n = genome length; k = user specified target binding length of probe; K*mer* = genome fragment or oligo of length = k. (Numerical value of K = k).

HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].

Using these samples as well as purified HPV plasmids and probes designed by PathogenMIPer, we performed an initial validation in the lab to evaluate specificity and sensitivity using both MIP assay [6] and pyrosequencing [2] results as a comparator.

The samples were subjected to PCR using GP5/GP6+ primers, followed by pyrosequencing [2]. The methods for conducting the MIP assays are as described previously [6] with the minor modifications. In brief, for the initial annealing reaction, 400 ng genomic DNA or ~1–100 pg HPV plasmids, ~5 fmol of each of the 24 probes, 0.05 units Ampligase (Epicentre, Madison, WI), and 0.5 units

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Table 1: The HPV plasmid types tested in the laboratory with MIPs designed with the PathogenMIPer software.

Types of HPV plasmids tested	Accession number
HPV 6	X00203
HPV 11	M14119
HPV 16	K02718
HPV 18	X05015
HPV 31	J04353
HPV 33	M12732
HPV 34	X74476
HPV 35	M74117
HPV 39	M38185
HPV 40	X74478
HPV 42	M73236
HPV 43	NC_005349
HPV 44	U31788
HPV 45	X74479
HPV 51	M62877
HPV 52	X74481
HPV 56	X74483
HPV 58	D90400
HPV 59	X77858
HPV 66	U31794
HPV 68	NC_004710
HPV 69	M73258
HPV 73	U21941
HPV 82	X94165

Stoffel fragment DNA polymerase (Applied Biosystems, Foster City, CA) in 10 μL of 20 mmol/L Tris-HCl (pH 8.3), 25 mmol/L KCl, 10 mmol/L $MgCl_2$, 0.5 mmol/L NAD, 0.01% Triton X-100 and 0.5 mM dGTP were incubated for 4 minutes at 20°C, 5 minutes at 95°C and then 15 minutes at 60°C, the reaction was cycled 10 cycles. Subsequently, 10 units exonuclease I and 200 units exonuclease III (Epicentre, Madison, WI) were added and the mixture was incubated for 60 minutes at 37°C and 20 minutes at 80°. Following exonucleolysis, the reaction was subjected to uracil depurination and cleavage with 2 units uracil-*N*-glycosylase (New England Biolabs, Ipswich, MA) in 20 μL of 1.6 mmol/L $MgCl_2$, 10 mmol/L Tris-HCl (pH 8.3), and 50 mmol/L KCl and incubated for 60 minutes at 37°C and 20 minutes at 80°C. To amplify the inverted probes, 1.5 units AmpliTaq Gold (Applied Biosystems), 10 pmol of each universal primer in 25 μL of 1.6 mmol/L $MgCl_2$, 10 mmol/L Tris-HCl (pH 8.3), 50 mmol/L KCl, and 112 μmol/L deoxynucleotide triphosphate (dNTP) were added to the genotyping reactions.

The reactions were amplified in 35 cycles of 95°C for 30 seconds, 55°C for 30 seconds, and 72°C for 10 seconds.

Microarray preparation

Microarrays were prepared using CodeLink activated slides (Amersham, Piscataway, NJ) with 5'amine-modified oligonucleotide. Oligonucleotides were printed onto microarray slides from a solution containing 1× printing buffer (50 mM sodium phosphate, pH 8.5), 20 μM probe using a microarrayer (BioDot, Inc., Irvine, CA). Positive and negative controls were printed on the microarray as well.

Each sample was printed in 4 replicates and 2 arrays were present on each chip. The post-printing processing of the microarray-chips were performed as recommended by the slide manufacturer.

Microarray hybridization

For the target hybridization step we used 50 μL of biotinylated PCR products, 1× hybridization buffer (100 mM MES, 1 M [Na+], 20 mM EDTA, 0.01 Tween 20) and 1.25× Denhardt's solution. The hybridization was performed at 42°C for 12–16 h. After hybridization, the microarray was washed with wash buffer (6× SSPE, 0.1% Tween 20) 2 times at 50°C for 2 min and once at room temperature for 2 min. The microarray was labeled for 10 min at 50°C with a solution containing streptavidin-allophycocyanin conjugated (1 mg/ml), 6× SSPE, 1× Denhardt's solution and 0.01% Tween 20. Following washing, 3 times in wash buffer, the microarray was assayed for fluorescent intensity at 635 nm using a GenePix 4000 fluorescent scanner (Axon Instrument, Foster City, CA) set to scan at 450 PMT. We used GenePix Pro software to determine the total fluorescent signal from each feature. To further confirm the results, 10 μl of the same PCR product that was used in microarray hybridization was sequenced by pyrosequencing as described by Gharizadeh et al [2].

The sensitivity (Sn) and specificity (Sp) of any system can be defined in terms of four outcomes – true positive (TP), true negatives (TN), false positives (FP), false negatives (FN) [17,18]. In our assay, the sensitivity is the fraction of actual positives which are predicted as positives, and specificity is the overall fraction of prediction that is correct. This correctness was checked by pyrosequencing method [2].

Results

Unique sequence generation

As described above, candidate homologous sequences were checked and evaluated, and the bad ones were eliminated (steps 1–6). Then, the average melting temperature of the candidates was calculated to check whether it was feasible to design MIPs with the specified Tm. Next, all candidates were checked for the middle base, and then for their Tm. The software designed total 4244 candidates for 105 HPV types, for a user specified Tm of 60°C (the software used 60 ± 4°C), length 50 bp and middle base G. On an average 40 candidates were generated for each of the 105 HPV type genomes. The number of candidates gener-

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ated for each genome varied from 30 to 75 depending on their genomic variability.

Candidate selection

As described above, in steps 4–6, the candidates for each HPV genotype target were checked against non-target genomes for their similarity. We checked the candidates of each HPV type against the genomes of other HPV types for similarity. The two homologous sites of the probes were evaluated in such a way that if they had any sequence matches in a non-target genome in the middle region, they incur much higher penalties than for the matches distal to the middle region. For each of the comparisons of the homologous sites of the probe against a non-target-genome, the total penalty score is checked against a threshold cut off value, set by the software based on the minimum mismatch percent specified by the user while setting up parameters for the design of MIPs. If the score exceeded the cutoff, the candidate was eliminated. When this filter was used against the candidate HPV probes generated in the previous step, PathogenMIPer returned a total of 2245 candidates, or 52% of the original candidates. The remaining 48% of the candidates were discarded in this step due to potential non-specific binding with non-target-genomes. The number of candidates returned per genome varied from 3 to 41 at the end of filtering.

Screen against the host genome

Finally (Steps 7–9), the best candidates were checked against the potential background or host genome through a remote BLAST and genome database on the NCBI server. Non-specific binding was reduced by making sure that the target-specific probe would not have more than 80% matches to the non-target genomes, or in their potential host genome. For the probes developed against 105 HPV types, the filtered candidates were subjected to BLAST against the human genome (the potential host), and PathogenMIPer eliminated 61 candidate sequences based on the matches in host genome, rendering more specificity for the assay. The software returned 2184 candidate probes for all the 105 types of HPV.

Tag placement

Once the homologous site construction is completed, the user can add predefined tag sequences to the homologous constructs. These tag sequences can be universal primers for the amplification of the binding signal, and/or molecular barcodes for the detection of the targets using tagArray (Affymetrix, Santa Clara, CA) or by sequencing methods such as pyrosequencing [2].

The tag sequences input by the user are added in the preferred order as shown in the figure 1. Figure 1 shows a well-constructed standard MIP consisting of six parts: two homologous constructs, two universal primers (one forward and one reverse), a restriction enzyme binding site and a molecular bar code sequence. These parts have to be constructed in a specific order in order for the MIP to work perfectly. This is done by the PathogenMIPer software interactively. The tags when added to the probe sequence may generate sequences complementary to probes of other targets included in the assay, resulting in cross hybridizations and oligo-dimer formations, which will render the results to be false positive. The PathogenMIPer software checks all the constructed probes, and eliminates the ones having problems in tags. The final selected probes are written in a file, saving the eliminated ones in a separate file. The user can look at the eliminated ones and can change the tags in those eliminated ones and later choose to include them in the assay. The user can follow and add individual steps or finish the design process in a single step.

Laboratory validation

The MIP assay was performed in 7 steps as depicted in figure1(A–E). The PathogenMIPer probes detected all 24 HPV types (100% sensitivity) when tested on plasmids with no false positives (100% specificity). In more complex clinical samples, the PathogenMIPer probes were able to produce distinct signals for the detection of single as well as multiple infections. Also, all 24 HPV types were detected in clinical samples (100% sensitivity as compared to conventional genotyping results) with no false positives (as compared to conventional genotyping techniques such as pyrosequencing). The data are shown in Table 2, 3. The pyrogram data for each of the samples were on par with the results of MIP assay.

Performance

Software performance of probe design is mainly limited by the amount of available memory, and the processor speed. The initial phase of generating candidate homologous sites (Steps 1–4) takes considerable processing time. In the example described here, this stage took ~3 hours. If more constraints are applied, the processing time will be increased, as more and more testing processes are done on the probe candidates. The number of targets and the length of each target affects the processing time as well. The total processing time is also depending on the number of candidates returned in the first step. When the number of targets increases, the processing time increases exponentially. Another major factor for the processing time is the divergence of the pathogen genomes. When the genomes of pathogens included in a MIP assay are more divergent, or distant, a greater number of candidates are generated and the processing time is longer.

The second phase of evaluating the candidates (Steps 5–7), is a very computationally intensive process, and the

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Table 2: The results of clinical samples tested with the HPV MIPs designed with PathogenMIPer.

Sample #	Results from MIP assay	Results from conventional genotyping
1) OM-1078	HPV-16	HPV-16
2) OM-1272	HPV-16	HPV-16
3) OM-1299	Negative	Negative
4) OM-1301	HPV-16	HPV-16
5) OM-1452	HPV-18	HPV-18
6) OM-1464	HPV-16	HPV-16
7) OM-1530	HPV-16	HPV-16
8) OM-1569	HPV-59	HPV-59
9) OM-1668	HPV-59	HPV-59
10) OM-1741	HPV-18	HPV-18
11) OM-1751	HPV-16	HPV-16
12) OM-1848	HPV-45	HPV-45
13) OM-1854	HPV-18	HPV-18
14) OM-1967	HPV-16	HPV-16
15) OM-1980	HPV-18	HPV-18
16) OM-2006	HPV-16	HPV-16
17) OM-2059	HPV-16	HPV-16
18) OM-2215	HPV-18	HPV-18
19) OM-2257	HPV-16	HPV-16
20) OM-2258	HPV-45	HPV-45

time taken for this step (~50 minutes in our case) also depends on the parameters specified by user. The last step, in which the sequences are checked against the host genome through a BLAST, was done on the genome database at NCBI server. The criteria for BLAST are set by the PathogenMIPer software and the BLAST software called upon is the current version running remotely on the NCBI server. Although this takes additional processing time (~9.5 hours in this example), it adds to the quality of the MIP assay by increasing uniqueness and reducing noise.

When used for designing 105 different types of human papilloma viruses, PathogenMIPer generated a complete pool of probe sequences in less than 15 hours. The software is quite flexible in allowing candidates generated in each of the steps to be viewed, checked and accessed for editing so that one can go back to any step in the process and revise the design without deleting the candidates of the previous design, although such interventions would of course be more time-consuming.

Table 3: Summary of results.

TP	TN	FP	FN	Sn	Sp
24	0	0	0	24/24 (100%)	20/20 (100%)

The sensitivity (Sn) and specificity (Sp) of any system can be defined in terms of four outcomes – true positive (TP), true negatives (TN), false positives (FP), false negatives (FN) [17, 18]. In our assay, the sensitivity is the fraction of actual positives which are predicted as positives, and specificity is the overall fraction of prediction that is correct. When the MIPs designed using PathogenMIPer were used in detection, it gave a sensitivity of 100% and a specificity of 100%.

Discussion

In preliminary tests with just 24 probes against 24 HPV genotypes, (i.e. one probe for each genotype present), we were able to sensitively detect all 24, with a lower limit of detection for purified plasmid as low as ~1 pg. In addition, we were able to detect multiple infections in samples containing HPV plasmids, without false positives, resulting in a specificity of 100%. Note that although PathogenMIPer designed 3 – 20 probes for each HPV type, this initial validation used only one probe per genotype. By relying on a single probe for the entire genome of HPV, which is ~8000 bp long, poor binding or even non-binding of the probe to the target would result, if mutations occur in the same locus chosen for the design of the MIP for these genotypes, leading to suboptimal results. A more complete diagnostic would necessarily anticipate such a problem by incorporating multiple probes for those subtypes whose genetic variation makes their identity more difficult to distinguish.

The PathogenMIPer system is extendable, with the addition of new modules and new design strategies. Because the quality requirements and other criteria for probes vary for different MIP assays, this software is able to support the design of different types of oligonucleotides, based on the constraints specified by the user. Although the processing time initially increases exponentially with the number of target genomes, this processing time levels off after a certain number of targets/genomes, as the software designs candidates by progressive elimination of non-specific candidates.

Although the PathogenMIPer software is a tool for the design of highly specific oligonucleotides for use in MIP assays, this system essentially serves as an *in silico multiplex test system*, whereby one can check the feasibility of designing a MIP assay for the specific targets one might want to include in a multiple detection technique. In the process of identifying unique specific sequences and adding tag sequences, universal primers, or cleavage sites to the complete probe design for a MIP assay, PathogenMIPer performs an efficient search for probes that have the highest probable success of producing a viable and robust MIP assay.

Conclusions

PathogenMIPer is a software for designing molecular inversion probes for detection of multiple target DNAs in a sample. This software simplifies development of MIP assays, enabling broader use of MIP technology in the detection through genotyping of pathogens that are complex, difficult-to-amplify, or present in multiple subtypes. PathogenMIPer facilitates large scale multiplex assays, without the need for PCR sample preparation before analysis. For multiple detection strategies where amplification

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by a common primer is not possible, the feasibility of developing a MIP assay can be interrogated through our *in silico* system prior to launching costly and time-consuming laboratory experiments. The system can be extended to design probes for new types of assays such as hairpin inversion probes. Extending the software by adding various modules for designing different types of primers and probes is under way.

Availability and requirements

PathogenMIPer software is available as an additional file with the article.

(See Additional files 1, 2, 3, 4, and 5).

Name: PathogenMIPer

OS: Windows

Language: Perl

Requirements: Internet connection for background checking.

Authors' contributions

ST designed and developed the software tool and drafted the manuscript. MK checked the software and helped to draft the manuscript. MA did the wet lab for validating the probes designed with PathogenMIPer software. RD helped to draft the manuscript. NP conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Additional material

Additional File 1

This lists all the instructions for downloading and running the software.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2105-7-500-S1.doc]

Additional File 2

This contains all the data files used for designing probes with the software and a subdirectory containing the result files obtained.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2105-7-500-S2.zip]

Additional File 3

It has two software executables, needed for running the software.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2105-7-500-S3.zip]

Additional File 4

It has two software executables, needed for running the software.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2105-7-500-S4.zip]

Additional File 5

It has two files, needed for running the software.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2105-7-500-S5.zip]

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PathogenMIPer_protocol.doc supplemental File

Download instructions:

1. Download all three zipped files.
2. Unzip them all into the same directory, so that all the exe files are under the same directory.

Note: A data file (a sample fasta file) and a file containing tags are included for testing.

Steps to run the PathogenMIPer application

1. Activate/ start the software by starting the PathogenMIPer.exe .
2. Then click on "Create a new project button". This will open an entry screen for initial parameters of MIPs design.
3. Give a new project name, folder where to create the project directory, and the project parameters – length of target binding part of the MIP, middle base, the region to be avoided while designing Mip (highly mutated/deleted part of genome)(starting and ending), melting temperature desired, fasta file where all genomes are stored. Example of initial entry screen is on Figure 1.

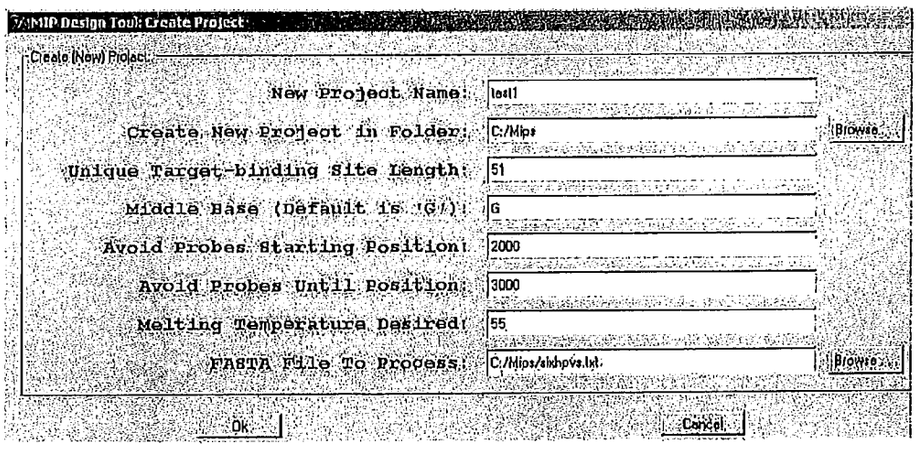


Figure 1. Example of creating project with initial parameters for designing MIPs candidates based on FASTA file sixhpvs.txt with 6 HPV genomes.

4. Once all parameters are set, then start the step of finding candidates for the MIPs, by pressing "Find probe candidates button". Example of running project "test1" is on Figure 2.

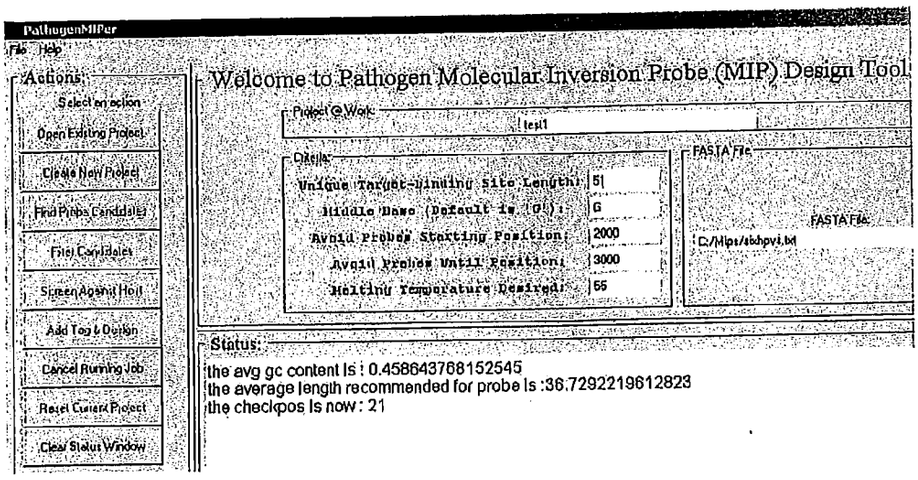
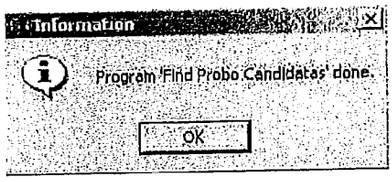


Figure 2. Running project with initial parameters to find and generate MIPs candidates.

5. It can run for several minutes or hours depending on the genome size and number of genomes and other design parameters. Status details are shown in the status window (see Figure 2). When finding job is finished, the status is displayed through a pop-up window (Figure 3).

Figure 3. Popup information after finishing finding of candidates.



6. The next step is to filter generated candidates by the now enabled button "Filter Candidates". The candidate file is located in the project subdirectory with the project name and extension ".cnd". In our example the file name is "test1.cnd" and file is located in C:\MIPs\test1\test1.cnd. This step is giving the minimum mismatch desired for the MIPs of one target genome, against the other targets in the assay (20 – 30% is ideal. The maximum that can be set is 50%).
Example of this entry window is on Figure 4.

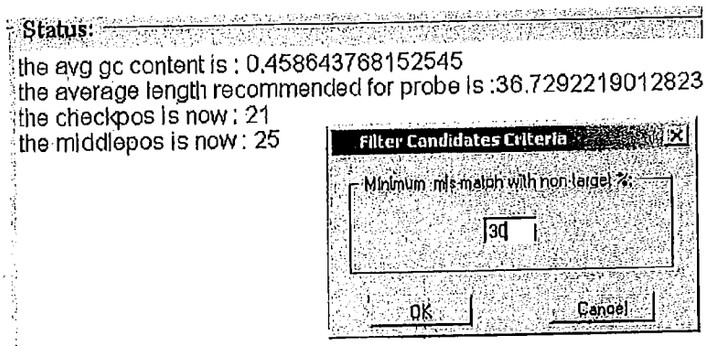


Figure 4. Popup entry window for filtering candidates with minimum percentage mis-match set to "30%" within target genomes.

7. When filtering candidates is finished a pop-up will inform user about its completion, see Figure 5. Filtered candidates are formatted in new file of the project directory. In our example the file name is test1.ftr located in C:\MIPs\test1\test1.ftr.

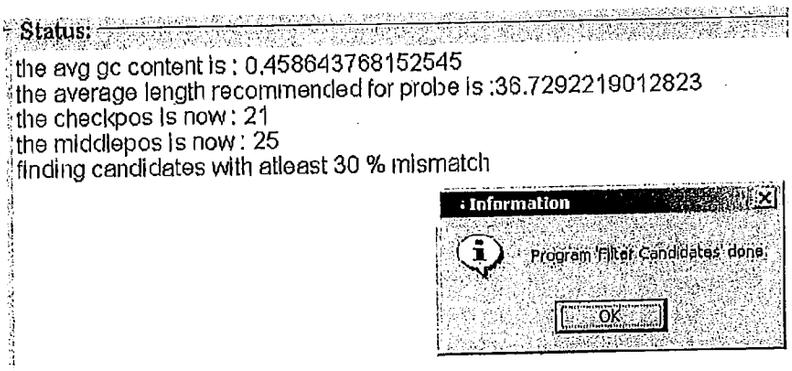


Figure 5. Popup information after finished filtering of candidates with 30% minimum mis-matoh.

8. Next step is blasting all the MIPs against the genome of potential host, or the background genome. Click the "Screen against host " button, and give the name of host, e.g. scientific name or biological name: Homo sapiens or human, see Figure 6.

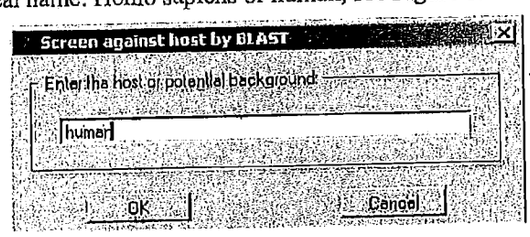


Figure 6. Popup window for screening candidates against "human" genome.

9. Blasting will run for a long time, because it is done remotely on the NCBI server against the database chosen by the user, see example on Figure 7.. Completion of the program is informed by the popup, see Figure 8 .

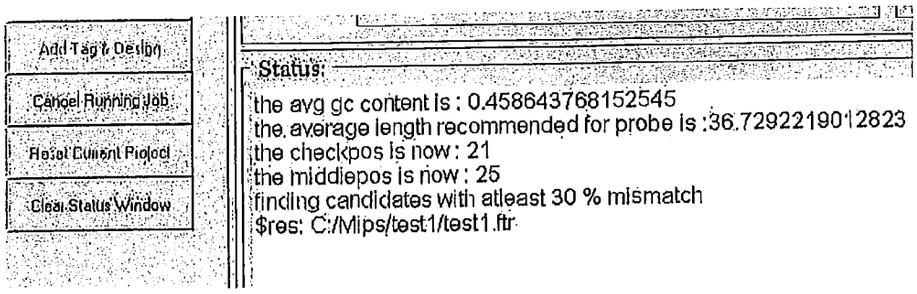
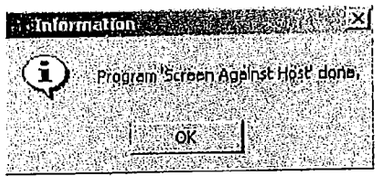


Figure 7. Example of running remote blast of test1 project with filtered FASTA candidates located in file C:\Mips\test1\test1.ftr.

Figure 8. Popup information after finishing blasting of candidates against "human" genome.



10. In the next step tags and primers are added to final probes as well as a cleavage site. This can be done by pressing "Add tag and design" button. In the input window (Figure 9) give the name of the tagfile, the universal primers in 5' -3' direction (very important), and the cleavage sequence in 5'-3'. The tagfile should be in the format, tagID followed by tag sequence separated by colon (:). The tag file should have one tag/barcode for each of the genomes included in the fasta file for the assay.

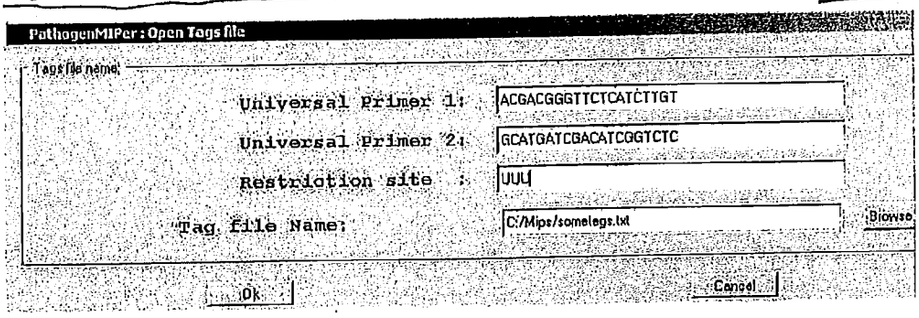


Figure 9. Input parameters for adding final tags to MIP probes.

11. After adding tags is completed, program informs user by the pop-up and shows names of generated probes in the status window (Figure 10). Final file testI.prb is located in project subdirectory (e.g. C:\Mips\testI\test1.prb) as usual.

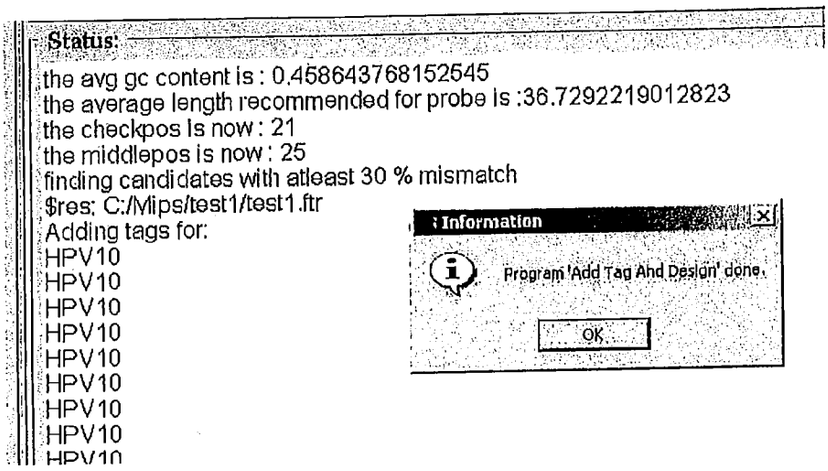


Figure 10. Information popup after finishing adding tags and primers to probes.

The whole design processing does not need to be done in a single stretch. Program can be stopped after finishing of any step. You can always open a project and continue working on the project until finishing all steps.
You can view the intermediary results of the progress during the design process. There is an intermediary file created after each step during the design. The file created at the end of "find candidates" has name: "project_name.cnd". The file at the end of "filter candidates" has name: "project name.ftr". The file after "screen against host" has name "project_name.res", and finally the file after "adding tags" has name "project_name.prb". After adding tags, the probes with problems in the tag region (primers or molecular barcode) are put in a separate file with name, "project_name_bad.prb". None of these files are supposed to be edited by the users, because this will halt the further steps in the design process.

The data in the final resulting file, i.e. the probe file are tab separated and are easily viewed as a word document. They can be imported into an excel file for further use by the user. Each of the intermediary files have the genotype accession number or the id number with some features of the sequence and the probe sequence itself. The finally assembled ready to order probes rendered in the .prb file have the details in the order - genotype / id, location of the MIP in target genome, tagID, homologue2 of the probe, followed by the two primer sequences separated by the cleavage/restriction sequence, and the homologue 1 of the probe.

test1.prb supplemental file: all probes for a given locus/genome have the same 'tag' sequence

ID	Position	tagID homologue1	homologue2	tm1	tm2	tag sequences undesired matches	
HPV10	58	YML001W	tagcatctgcagaagctatgtccatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatggggtacatataaaacaaggccc	55	57	15	
HPV10	61	YML001W	catctgcagaagctatgtccatgggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggtacatataaaacaaggcccgta	55	58	15	
HPV10	84	YML001W	ggtgcacaggaacccagaaacatatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagcatctgcagaagctatgtccat	55	58	17	
HPV10	85	YML001W	gtgcacaggaacccagaaacatattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagcatctgcagaagctatgtccatg	57	57	17	
HPV10	86	YML001W	tgcacaggaacccagaaacatattgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcatctgcagaagctatgtccatgg	58	55	17	
HPV10	88	YML001W	cacaggaacccagaaacatattgctGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatctgcagaagctatgtccatgggt	57	57	17	
HPV10	93	YML001W	gaacccagaaacatattgcttttgtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagaagctatgtccatgggtgcaca	58	53	17	
HPV10	94	YML001W	aacccagaaacatattgcttttgtgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaagctatgtccatgggtgcacag	58	52	17	
HPV10	117	YML001W	tgtagaaattgtggaatacctttggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggaacccagaaacatattgctttt	52	52	17	
HPV10	122	YML001W	aaattgtggaatacctttggaggacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcccagaaacatattgcttttgtgta	52	53	17	
HPV10	144	YML001W	gaccttcgcctgtgctgtatattttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtagaaattgtggaatacctttgga	52	57	17	
HPV10	145	YML001W	accttcgcctgtgctgtatattttgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagaaattgtggaatacctttggag	52	55	19	
HPV10	192	YML001W	gaattggcagcatttgcacttagagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttgcacaaaacagctgaccgcagc	58	55	21	
HPV10	215	YML001W	agaattatatttggtgtggagagcgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcggaattggcagcatttgcactta	57	53	21	
HPV10	217	YML001W	aattatatttggtgtggagagcgggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaattggcagcatttgcacttaga	55	55	19	

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HPV10 289 YML001W tacgacgcctaaaatattgggactaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacggtgtttactcctacagggcatt	57	55	15
HPV10 293 YML001W acgcctaaaatattgggactattcaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtttactcctacagggcattgtac	55	53	15
HPV10 308 YML001W ggactattcatattatgtagaaggtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcattgtacgacgcctaaaatatt	53	52	17
HPV10 387 YML001W tgtcacaaaccgctggtaagggaagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatacacagctgatcagatgctacat	53	58	17
HPV10 389 YML001W tcacaaaccgctggtaagggaagaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacacagctgatcagatgctacatgt	55	58	19
HPV10 437 YML001W gcgacgactgcacaaaatatcagggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaaaagacagacatcgtaacgaac	53	58	21
HPV10 438 YML001W cgacgactgcacaaaatatcagggtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaaaagacagacatcgtaacgaacg	53	58	21
HPV10 461 YML001W gtactggagaggtagttgtgagtatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcggcgacgactgcacaaaatatcag	58	57	17
HPV10 462 YML001W tactggagaggtagttgtgagtattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcgacgactgcacaaaatatcagg	58	55	15
HPV10 467 YML001W gagaggtagttgtgagtattgctggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgactgcacaaaatatcagggtact	55	57	19
HPV10 468 YML001W agaggtagttgtgagtattgctggtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgactgcacaaaatatcagggtactg	55	57	21
HPV10 470 YML001W aggtagttgtgagtattgctggtcaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgcacaaaatatcagggtactgga	55	57	21
HPV10 472 YML001W gtagttgtgagtattgctggtcacgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcacaaaatatcagggtactggaga	55	57	21
HPV10 473 YML001W tagttgtgagtattgctggtcacgaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacaaaatatcagggtactggagag	55	57	21
HPV10 531 YML001W aattgagtcttgcaccagaggatatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccgcatcccacagtaaaagatatc	55	55	17
HPV10 538 YML001W tcttgcaccagaggatatccctgtaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcccacagtaaaagatatcgaattga	52	58	17
HPV10 549 YML001W aggatatccctgtatgcaatgtgcaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagatatcgaattgagtcttgcacca	53	57	15
HPV10 552 YML001W atatccctgtatgcaatgtgcaattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatcgaattgagtcttgcaccagag	55	53	15

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HPV10	561	YML001W	tatgcaatgtgcaattagatgaagaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgagtcttgcaccagaggatatccct				58	52 15
HPV10	582	YML001W	aagaagattatacagatgcggtggaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccctgtatgcaatgtgcaattagat				53	55 17
HPV10	603	YML001W	tggaaccagcacaacaagcgtatagGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagatgaagaagattatacagatgcg				52	57 17
HPV10	605	YML001W	gaaccagcacaacaagcgtatagggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgaagaagattatacagatgcggt				52	58 17
HPV10	606	YML001W	aaccagcacaacaagcgtatagggtGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgaagaagattatacagatgcggtg				53	58 17
HPV10	621	YML001W	cgtatagggtggtaacagaatgtacGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagatgcggtggaaccagcacaacaa				58	55 15
HPV10	628	YML001W	ggtggtaacagaatgtacaaagtgtGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtggaaccagcacaacaagcgtata				57	55 17
HPV10	629	YML001W	gtggtaacagaatgtacaaagtgtaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggaaccagcacaacaagcgtatag				57	53 17
HPV10	630	YML001W	tggtaacagaatgtacaaagtgtagGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaaccagcacaacaagcgtatagg				58	52 17
HPV10	632	YML001W	gtaacagaatgtacaaagtgtagttGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaccagcacaacaagcgtatagggt				57	52 17
HPV10	639	YML001W	aatgtacaaagtgtagtttaccactGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaacaagcgtatagggtggtaaca				55	52 17
HPV10	643	YML001W	tacaaagtgtagtttaccactgcgaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaagcgtatagggtggtaacagaat				55	55 19
HPV10	650	YML001W	tgtagtttaccactgcgactggtggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatagggtggtaacagaatgtacaaa				52	58 19
HPV10	652	YML001W	tagtttaccactgcgactggtggtaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagggtggtaacagaatgtacaaagt				53	58 21
HPV10	674	YML001W	gtagagtgcagccacgcagatataaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtgtagtttaccactgcgactggt				57	58 21
HPV10	713	YML001W	ctgctactaggcacattgaagctcgGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacgcagatataagggcactggaaca				57	58 15
HPV10	716	YML001W	ctactaggcacattgaagctcgtgtGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagatataagggcactggaacagct				57	58 17
HPV10	751	YML001W	cgtgtaacaggacatggacgataatGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacattgaagctcgtgtgtcctcgct				58	57 17

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HPV10	896	YML001W	gacgaagcaggggaagactttgtagGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatctagtgatgatgatgaggagga				53	58	21
HPV10	897	YML001W	acgaagcaggggaagactttgtagaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatctagtgatgatgatgaggaggag				55	58	21
HPV10	903	YML001W	caggggaagactttgtagactttatGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgatgatgaggaggaggacgaa				57	55	19
HPV10	906	YML001W	gggaagactttgtagactttatagaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgatgaggaggaggacgaagca				58	53	19
HPV10	921	YML001W	actttatagatgatactaggtcgctGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggacgaagcaggggaagactttgta				58	53	19
HPV10	930	YML001W	atgatactaggtcgctaggggatggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggggaagactttgtagactttata				52	58	15
HPV10	955	YML001W	acaggaagtggcacaggaactgttcGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgatactaggtcgctaggggatg				58	58	15
HPV10	986	YML001W	cagacagctgcagatgacgatgtagGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagtggcacaggaactgttccagca				58	58	17
HPV10	1014	YML001W	tgcagactgtaaaacgaaagtttgcGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacagctgcagatgacgatgtagct				58	53	21
HPV10	1016	YML001W	cagactgtaaaacgaaagtttgcacGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagctgcagatgacgatgtagctgt				58	53	21
HPV10	1070	YML001W	caagccagcatagaacatgaactaaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtccttatttcagccccgtgtgtga				58	55	17
HPV10	1074	YML001W	ccagcatagaacatgaactaagcccGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttatttcagccccgtgtgtgagcaa				57	57	17
HPV10	1179	YML001W	gccaaacacaggtggatacggaatcGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtttgagctaccggacagtggctat				58	58	21
HPV10	1193	YML001W	gatacggaatcgggaccaaaacaggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacagtggctatggccaaacacaggt				58	58	17
HPV10	1199	YML001W	gaatcgggaccaaaacaggtacaggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgctatggccaaacacaggtggatac				58	58	17
HPV10	1200	YML001W	aatcgggaccaaaacaggtacagggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctatggccaaacacaggtggatacg				58	58	17
HPV10	1206	YML001W	gaccaaaacaggtacagggcagtagGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccaaacacaggtggatacggaatcg				58	58	17
HPV10	1207	YML001W	accaaaacaggtacagggcagtagtGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaaacacaggtggatacggaatcgg				58	58	15

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HPV10	1217	YML001W	gtacagggcagtagtgaaacgcaagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggatacggaatcgggaccaaaaca	57	58	17
HPV10	1253	YML001W	gatgatgatgaggggagtgtggtacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtagtgaaacgcaagatggccgaca	58	58	17
HPV10	1254	YML001W	atgatgatgaggggagtgtggtacaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagtgaaacgcaagatggccgacag	58	58	17
HPV10	1275	YML001W	tacagagcacacttgacacaggcaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaggatgatgatgaggggagtgtg	58	58	19
HPV10	1428	YML001W	gagcaggtggcgtggtagaaatattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttacaaagtacaagcactggcaag	55	58	17
HPV10	1429	YML001W	agcaggtggcgtggtagaaatattaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttacaaagtacaagcactggcaagg	55	57	15
HPV10	1434	YML001W	gtggcgtggtagaaatattaagagcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagtacaagcactggcaagggagca	58	55	17
HPV10	1456	YML001W	agccagcaataagaaagcaactctaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcaggtggcgtggtagaaatattaa	55	55	21
HPV10	1458	YML001W	ccagcaataagaaagcaactctactGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggtggcgtggtagaaatattaaga	53	55	21
HPV10	1601	YML001W	gcagagggcataaagaccctaatacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtgttcggggtgttttgcacagt	58	57	15
HPV10	1602	YML001W	cagagggcataaagaccctaatacaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgttcggggtgttttgcacagtg	58	57	17
HPV10	1616	YML001W	accctaatacaaccattgtgtgattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttgcacagtggcagagggcataaa	57	53	19
HPV10	1638	YML001W	attatgcacacatacaagtgctaccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaagaccctaatacaaccattgtgt	52	53	19
HPV10	1658	YML001W	ctaccatgccaatggggaatgacagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgtgattatgcacacatacaagt	52	58	17
HPV10	1666	YML001W	ccaatggggaatgacagtgcttatgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatgcacacatacaagtgctaccat	53	57	15
HPV10	1679	YML001W	acagtgcttatgctggtacggtacaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagtgctaccatgccaatggggaat	57	58	15
HPV10	1685	YML001W	cttatgctggtacggtacaaacgtgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaccatgccaatggggaatgacagt	57	57	17
HPV10	1691	YML001W	ctggtacggtacaaacgtgccaaaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccaatggggaatgacagtgcttat	57	58	15

Petitioner Illumina, Inc., EX1003, p. 1051

HPV10	1695	YML001W	tacggtacaaacgtgccaaaaacagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatggggaatgacagtgcttatgctg	57	55	17
HPV10	1699	YML001W	gtacaaacgtgccaaaaacagggaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaatgacagtgcttatgctggtac	57	57	17
HPV10	1700	YML001W	tacaaacgtgccaaaaacagggaaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaatgacagtgcttatgctggtacg	57	55	17
HPV10	1708	YML001W	tgccaaaaacagggaaacagtggctGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgcttatgctggtacggtacaaac	57	58	15
HPV10	1710	YML001W	ccaaaaacagggaaacagtggctaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcttatgctggtacggtacaaacgt	57	57	17
HPV10	1722	YML001W	aaacagtggctaaaggcttaagcacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacggtacaaacgtgccaaaaacagg	57	55	17
HPV10	1730	YML001W	gctaaaggcttaagcacattattaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacgtgccaaaaacagggaaacagt	55	52	15
HPV10	1744	YML001W	cacattattaaatgtaccggaaagcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagggaaacagtggctaaaggcttaa	55	52	19
HPV10	1910	YML001W	gaggatgcgcagtttagcctttcagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcagacaatggtgggacatgcaat	58	58	17
HPV10	1911	YML001W	aggatgcgcagtttagcctttcagaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagacaatggtgggacatgcaatg	58	58	17
HPV10	1913	YML001W	gatgcgcagtttagcctttcagagaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagacaatggtgggacatgcaatgga	57	58	19
HPV10	1914	YML001W	atgcgcagtttagcctttcagagatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacaatggtgggacatgcaatggag	58	57	17
HPV10	1917	YML001W	cgcagtttagcctttcagagatggtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaatggtgggacatgcaatggaggat	57	58	19
HPV10	1982	YML001W	ctggcatacgagtatgcactgattgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccatgatattacagacgagagcac	55	57	21
HPV10	1986	YML001W	catacgagtatgcactgattgctgaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatattacagacgagagcacgctg	57	57	21
HPV10	3027	YML001W	acattgcgggacacatcacgtgaaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaagtgcctatgcacacgaaccctg	58	58	21
HPV10	3100	YML001W	ttgaagtcagatatgatggagacgaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgctggaaaaaaaggggataact	55	55	19
HPV10	3103	YML001W	aagtcagatatgatggagacgaatcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctggaaaaaaaggggataactgtt	53	53	17

Petitioner Illumina, Inc., EX1003, p. 1052

HPV10	3106	YML001W	tcagatatgatggagacgaatctaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaaaaaaggggataactgttgaa	52	53	17
HPV10	3115	YML001W	atggagacgaatctaaagccatgtgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggggataactgttgaagtcagatat	53	55	17
HPV10	3121	YML001W	acgaatctaaagccatgtgctatgtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaactgttgaagtcagatatgatgga	52	55	17
HPV10	3124	YML001W	aatctaaagccatgtgctatgtacaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgttgaagtcagatatgatggagac	53	53	17
HPV10	3133	YML001W	ccatgtgctatgtacaatggagggaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagatatgatggagacgaatctaaa	52	58	17
HPV10	3138	YML001W	tgctatgtacaatggagggaactttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgatggagacgaatctaaagccat	53	55	17
HPV10	3152	YML001W	gagggaactttatgtgcagaactatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctaaagccatgtgctatgtacaat	52	55	17
HPV10	3153	YML001W	agggaactttatgtgcagaactataGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctaaagccatgtgctatgtacaatg	53	53	17
HPV10	3155	YML001W	ggaactttatgtgcagaactatagtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaagccatgtgctatgtacaatgga	53	53	17
HPV10	3157	YML001W	aactttatgtgcagaactatagtgaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagccatgtgctatgtacaatggagg	57	52	17
HPV10	3171	YML001W	aactatagtgacgatagatgggtgaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacaatggagggaactttatgtgca	53	55	17
HPV10	3184	YML001W	atagatgggtgaaggtgccaggaaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactttatgtgcagaactatagtgac	52	58	17
HPV10	3188	YML001W	atgggtgaaggtgccaggaaaagtcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatgtgcagaactatagtgacgata	52	58	17
HPV10	3192	YML001W	gtgaaggtgccaggaaaagtctcatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcagaactatagtgacgatagatg	53	58	17
HPV10	3193	YML001W	tgaaggtgccaggaaaagtctcataGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagaactatagtgacgatagatgg	55	57	17
HPV10	3195	YML001W	aaggtgccaggaaaagtctcatacgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaactatagtgacgatagatgggt	53	57	17
HPV10	3198	YML001W	gtgccaggaaaagtctcatacgaggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactatagtgacgatagatgggtgaa	53	58	17
HPV10	3199	YML001W	tgccaggaaaagtctcatacgagggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctatagtgacgatagatgggtgaag	55	58	17

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HPV10 3201 YML001W ccaggaaaagtctcatacgagggtcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatagtgacgatagatgggtgaaggt	55	58	17
HPV10 3309 YML001W gaggtacatgtgggaggcaaagtaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtatatggggaaacaggcaaatg	55	58	17
HPV10 3310 YML001W aggtacatgtgggaggcaaagtaatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtatatggggaaacaggcaaatgg	55	57	15
HPV10 3312 YML001W gtacatgtgggaggcaaagtaattcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatatggggaaacaggcaaatggga	55	55	15
HPV10 3313 YML001W tacatgtgggaggcaaagtaattcaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatatggggaaacaggcaaatgggag	57	55	15
HPV10 3321 YML001W ggaggcaaagtaattcaccatgatgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaacaggcaaatgggaggtacatgt	55	55	19
HPV10 3322 YML001W gaggcaaagtaattcaccatgatgcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacaggcaaatgggaggtacatgtg	57	55	19
HPV10 3323 YML001W aggcaaagtaattcaccatgatgcaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaggcaaatgggaggtacatgtgg	58	55	19
HPV10 3325 YML001W gcaaagtaattcaccatgatgcattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggcaaatgggaggtacatgtggga	58	53	19
HPV10 3331 YML001W taattcaccatgatgcatttgacccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgggaggtacatgtgggaggcaaa	58	53	17
HPV10 3343 YML001W atgcatttgaccctgtatctagcacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgggaggcaaagtaattcaccat	55	55	15
HPV10 3346 YML001W catttgaccctgtatctagcacacgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggaggcaaagtaattcaccatgat	55	57	15
HPV10 3365 YML001W cacacgagaaatatccactcctggaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatgatgcatttgaccctgtatcta	53	58	17
HPV10 3371 YML001W agaaatatccactcctggacctgtgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcatttgaccctgtatctagcacac	57	57	17
HPV10 3373 YML001W aaatatccactcctggacctgtgtgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatttgaccctgtatctagcacacga	55	57	17
HPV10 3760 YML001W aaaaccaggcagcgtttgtaacgctGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacatggaggtggtcttgtgagtca	58	58	15
HPV10 3768 YML001W gcagcgtttgtaacgctttggtataGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtggtcttgtgagtcagaaaacca	57	57	15
HPV10 3769 YML001W cagcgtttgtaacgctttggtatacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtggtcttgtgagtcagaaaaccag	57	55	15

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HPV10	3772	YML001W	cgtttgtaacgctttggtataccagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtcttgtgagtcagaaaaccaggca	57	55	15
HPV10	3774	YML001W	tttgtaacgctttggtataccagcgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttgtgagtcagaaaaccaggcagc	58	55	15
HPV10	3783	YML001W	ctttggtataccagcgatacacagcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagaaaaccaggcagcgtttgtaac	57	57	17
HPV10	3788	YML001W	gtataccagcgatacacagcgtactGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaccaggcagcgtttgtaacgcttt	57	58	15
HPV10	3797	YML001W	cgatacacagcgtactgaatttcttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcgtttgtaacgctttggtatacca	55	55	15
HPV10	3799	YML001W	atacacagcgtactgaatttcttaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtttgtaacgctttggtataccagc	55	52	13
HPV10	3844	YML001W	gcatacaagtgattttggggtatatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcttaatgttgtaaaggttcccct	53	53	17
HPV10	3845	YML001W	catacaagtgattttggggtatatgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttaatgttgtaaaggttcccctg	55	52	17
HPV10	3977	YML001W	ctgctgctgtgtttgttttggctgtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgactacattgctgggctttttttgt	53	58	17
HPV10	4101	YML001W	tcaacacataggtctcacaatgtatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaaattgtgacacgtattgtacag	52	53	17
HPV10	4152	YML001W	tgaccatcctgtattgttgtttgagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctcttatattaagagatcacactg	52	53	15
HPV10	4180	YML001W	ggggacgtgtatttactactgtgtgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccatcctgtattgttgtttgagcc	55	57	15
HPV10	4181	YML001W	gggacgtgtatttactactgtgtgtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccatcctgtattgttgtttgagccg	57	57	15
HPV10	4182	YML001W	ggacgtgtatttactactgtgtgtaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatcctgtattgttgtttgagccgg	57	55	15
HPV10	4183	YML001W	gacgtgtatttactactgtgtgtaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcctgtattgttgtttgagccggg	57	53	15
HPV10	4184	YML001W	acgtgtatttactactgtgtgtaatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctgtattgttgtttgagccgggg	58	52	15
HPV10	4340	YML001W	tgctattgtggcaccattctttttcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgttgttgttgtgtgtaccctagt	53	53	17
HPV10	4513	YML001W	caccaccttggcagatcgcattttgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccagatgttattcccaaagtagagg	55	58	17

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HPV10	4543	YML001W	gggtagccttggtgtatatttggggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccttggcagatcgcattttgcagt				57	58 15
HPV10	4544	YML001W	ggtagccttggtgtatatttgggggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccttggcagatcgcattttgcagtg				58	58 15
HPV10	4545	YML001W	gtagccttggtgtatatttgggggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttggcagatcgcattttgcagtgg				58	58 15
HPV10	4546	YML001W	tagccttggtgtatatttgggggcGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttggcagatcgcattttgcagtggg				58	58 15
HPV10	4557	YML001W	tatatttgggggcctaggcattggGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcattttgcagtggggtagccttggt				58	58 15
HPV10	4638	YML001W	gcactgttgtggatgttagtgttccGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtatgttcctatcagtacacgacct				55	57 15
HPV10	4639	YML001W	cactgttgtggatgttagtgttcctGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatgttcctatcagtacacgacctg				55	57 15
HPV10	4644	YML001W	ttgtggatgttagtgttcctgccagGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctatcagtacacgacctggcact				58	57 17
HPV10	4670	YML001W	cctcctgttgttattgagcctgtagGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgtggatgttagtgttcctgccag				57	57 15
HPV10	4731	YML001W	actccagcattattaattcagggtcGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccttccattgtaaatttgttggag				52	53 15
HPV10	5169	YML001W	tgtttgaaccggaggatgaaacaatGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctccttgttaacatttgacaatcct				52	55 19
HPV10	5181	YML001W	aggatgaaacaatcatattcgaacgGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatttgacaatcctgtgtttgaaccg				53	52 17
HPV10	5183	YML001W	gatgaaacaatcatattcgaacgtcGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgacaatcctgtgtttgaaccgga				55	52 17
HPV10	5394	YML001W	ccccaatcgaggacattgaaatggaGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttactatcaggaccttagccctata				53	58 17
HPV10	5405	YML001W	gacattgaaatggaacctttacttgGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccttagccctatagccccaatcga				58	52 15
HPV10	5412	YML001W	aaatggaacctttacttgctccagcGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccctatagccccaatcgaggacatt				58	55 15
HPV10	5418	YML001W	aacctttacttgctccagctgcctcGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagccccaatcgaggacattgaaatg				57	58 13
HPV10	5436	YML001W	ctgcctctgacactatttatgacatGTACGTGGAGATCGACATAA		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgaaatggaacctttacttgctcca				53	55 15

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HPV10 5439 YML001W cctctgacactatttatgacattttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaatggaacctttacttgctccagct	55	52	17
HPV10 5487 YML001W ttgcttttacagagggatatcgtagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttttgctgatgttgatgatggtgat	52	53	15
HPV10 5499 YML001W agggatatcgtagtaccacacagtcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgatggtgatgttgcttttaca	52	57	15
HPV10 5501 YML001W ggatatcgtagtaccacacagtccaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgatggtgatgttgcttttacaga	52	58	15
HPV10 5502 YML001W gatatcgtagtaccacacagtccagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatggtgatgttgcttttacagag	53	57	15
HPV10 5503 YML001W atatcgtagtaccacacagtccaggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatggtgatgttgcttttacagagg	55	57	15
HPV10 5509 YML001W tagtaccacacagtccaggggatatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgttgcttttacagagggatatc	53	58	15
HPV10 5512 YML001W taccacacagtccaggggatataatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttgcttttacagagggatatcgta	53	57	15
HPV10 5607 YML001W ttgatgtaactttacatactgggccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtaacaattccctttgtgtctcct	53	53	19
HPV10 5634 YML001W atattgtactacctacttcagcacaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgtaactttacatactgggcct	53	53	17
HPV10 5712 YML001W atggcggggatttctatctttggccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgacaccacccattatgtgtacata	53	58	15
HPV10 5716 YML001W cggggatttctatctttggcctgttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccacccattatgtgtacatagatg	53	58	15
HPV10 5718 YML001W gggatttctatctttggcctgttacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacccattatgtgtacatagatggc	55	55	15
HPV10 5719 YML001W ggatttctatctttggcctgttaccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacccattatgtgtacatagatggcg	55	55	15
HPV10 5720 YML001W gatttctatctttggcctgttacctGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcccattatgtgtacatagatggcgg	57	55	15
HPV10 5721 YML001W atttctatctttggcctgttaccttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccattatgtgtacatagatggcggg	57	53	15
HPV10 5735 YML001W cctgttacctttcacttctcccgacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagatggcggggatttctatctttg	55	58	15
HPV10 5739 YML001W ttacctttcacttctcccgacatcgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggcggggatttctatctttggcct	58	57	15

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HPV10	5764	YML001W	tcgccgtaaacgtgtctcatattttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttacctttcacttctcccgacatc	57	55	17
HPV10	5767	YML001W	ccgtaaacgtgtctcatatttttttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacctttcacttctcccgacatcgtc	58	52	21
HPV10	5807	YML001W	gcgctctagtgacaacttggtgtacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatatttttttgcagatggcactct	52	58	19
HPV10	5808	YML001W	cgctctagtgacaacttggtgtaccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatatttttttgcagatggcactctg	52	58	19
HPV10	5810	YML001W	ctctagtgacaacttggtgtacctgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatttttttgcagatggcactctggc	55	57	19
HPV10	5908	YML001W	gcacttcacggttgcttactgtaggGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacgcaccaacatttactattatgca	52	58	15
HPV10	5918	YML001W	gttgcttactgtaggccatccatatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatttactattatgcaggcacttcac	52	57	15
HPV10	5919	YML001W	ttgcttactgtaggccatccatattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttactattatgcaggcacttcacg	53	55	15
HPV10	5922	YML001W	cttactgtaggccatccatattttcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactattatgcaggcacttcacggtt	55	53	15
HPV10	5929	YML001W	taggccatccatattttcctataccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcaggcacttcacggttgcttact	58	53	15
HPV10	5932	YML001W	gccatccatattttcctatacctaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggcacttcacggttgcttactgta	57	53	15
HPV10	5933	YML001W	ccatccatattttcctatacctaagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcacttcacggttgcttactgtag	58	52	15
HPV10	5958	YML001W	tcaagtaacaataaggtagatgtccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccatccatattttcctatacctaa	52	52	17
HPV10	5988	YML001W	gtatctgcatttcaatatagggtgtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtaacaataaggtagatgtccccaa	53	53	15
HPV10	5989	YML001W	tatctgcatttcaatatagggtgttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaacaataaggtagatgtccccaag	53	52	17
HPV10	5995	YML001W	catttcaatatagggtgtttcgggtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaggtagatgtccccaaggtatct	55	55	15
HPV10	6019	YML001W	tgcggttgcctgaccctaataagttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcatttcaatatagggtgtttcgg	53	58	17
HPV10	6023	YML001W	gttgcctgaccctaataagtttggaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttcaatatagggtgtttcgggtgc	55	57	17

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HPV10	6024	YML001W	ttgcctgaccctaataagtttggacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttcaatatagggtgtttcgggtgcg	57	55	17
HPV10	6171	YML001W	ctagaggacacagaaaactctaataGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcagtggacaccctctatataataa	52	53	15
HPV10	6175	YML001W	aggacacagaaaactctaatatagcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggacaccctctatataataagcta	52	52	17
HPV10	6409	YML001W	gggccatggactttactgctttacaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtgatatggtggacactggctat	57	58	19
HPV10	6410	YML001W	ggccatggactttactgctttacaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtgatatggtggacactggctatg	58	57	19
HPV10	6411	YML001W	gccatggactttactgctttacaatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgatatggtggacactggctatgg	58	55	19
HPV10	6412	YML001W	ccatggactttactgctttacaattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatatggtggacactggctatggg	58	53	19
HPV10	6467	YML001W	ccaatctacttgtaaatatccagatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagtctgacgtgcctatagatattt	52	52	17
HPV10	6642	YML001W	cgagacgttggtagtgctgtgtataGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcatattaaagagcaacggtggggg	57	58	17
HPV10	6644	YML001W	agacgttggtagtgctgtgtatagcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatattaaagagcaacggtgggggc	58	57	15
HPV10	6739	YML001W	cccaggggcacaacaatggtatatgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaataagccatattggctgcggcgg	58	58	15
HPV10	6764	YML001W	ctgggctaaccaattgtttgttactGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcccaggggcacaacaatggtatat	58	55	15
HPV10	6880	YML001W	aatatttgaggcacggagaggaataGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacgtatgacgccaccaaatttaaa	52	55	15
HPV10	6937	YML001W	taacattgaccccggatattatggcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagttcatttttcagttgtgtaag	52	55	15
HPV10	6994	YML001W	aggattggaactttgggttaactttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcacaccatgaatagtagtttattg	52	53	17
HPV10	6997	YML001W	attggaactttgggttaactttgccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaccatgaatagtagtttattggag	52	53	17
HPV10	7011	YML001W	ttaactttgccaccgtccactagctGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtttattggaggattggaactttgg	53	58	15
HPV10	7026	YML001W	tccactagcttggaggacacatataGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaactttgggttaactttgccacc	57	57	17

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HPV10	7034	YML001W	cttggaggacacatatagattttgGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggttaactttgccaccgtccacta	58	52	15
HPV10	7038	YML001W	gaggacacatatagattttgtcctGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaactttgccaccgtccactagctt	57	53	15
HPV10	7039	YML001W	aggacacatatagattttgtcctcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaactttgccaccgtccactagcttg	58	52	15
HPV10	7102	YML001W	agaagcaggatccctatgcaaaactGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgtcagaaagatacacccccacc	58	57	17
HPV10	7107	YML001W	caggatccctatgcaaaacttaactGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaaagatacacccccaccgagaa	58	55	17
HPV10	7138	YML001W	acgtagatcttaaggataggttttcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccctatgcaaaacttaacttttgg	52	52	15
HPV10	7141	YML001W	tagatcttaaggataggttttccctGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctatgcaaaacttaacttttgggac	52	53	15
HPV10	7144	YML001W	atcttaaggataggttttccctggaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcaaaacttaacttttgggacgta	52	55	17
HPV10	7153	YML001W	ataggttttccctggacctgtctcaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaacttttgggacgtagatcttaag	52	58	13
HPV10	7157	YML001W	gttttccctggacctgtctcagtttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttttgggacgtagatcttaaggata	52	58	15
HPV10	7173	YML001W	tctcagtttcccctgggacgaaaatGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttaaggataggttttccctggacct	55	58	13
HPV10	7355	YML001W	ctgttaataggtgtttgtaatgtctGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgtgcatatttgtgtatgtggttg	52	52	17
HPV10	7365	YML001W	gtgtttgtaatgtctatgtatgtgtGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgtgtatgtggttggctgttaata	52	52	19
HPV10	7518	YML001W	gtcaggagaccgatttcggtacaagGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctgtgagtaagtaaggttgttcta	53	58	17
HPV10	7519	YML001W	tcaggagaccgatttcggtacaagaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgtgagtaagtaaggttgttctag	53	58	17
HPV10	7523	YML001W	gagaccgatttcggtacaagatggcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgagtaagtaaggttgttctaggtca	53	58	19
HPV10	7524	YML001W	agaccgatttcggtacaagatggccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtaagtaaggttgttctaggtcag	53	58	19
HPV10	7579	YML001W	tcatgctgatctatatcctgcgaccGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttccaggtgtgcacaccaccaatta	57	57	15

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HPV10 7606 YML001W ccctgtcacgccatttttttggctaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatgctgatctatatcctgcgacct	57	58	15
HPV10 7611 YML001W tcacgccatttttttggctaagattGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatctatatcctgcgacctgccct	58	53	15
HPV10 7681 YML001W cacggcaaactgtctccattgcaaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtttattgctgtatcatgctttctg	52	58	15
HPV10 7685 YML001W gcaaactgtctccattgcaaatttaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattgctgtatcatgctttctggcac	55	53	15
HPV10 7686 YML001W caaactgtctccattgcaaatttaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgctgtatcatgctttctggcacg	57	52	15
HPV10 7693 YML001W tctccattgcaaatttaacagcttcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcatgctttctggcacggcaaact	57	52	15
HPV10 7702 YML001W caaatttaacagcttctgggcaccaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctggcacggcaaactgtctccatt	58	57	15
HPV10 7720 YML001W ggcaccaacttattatgactactttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctccattgcaaatttaacagcttct	52	53	17
HPV10 7721 YML001W gcaccaacttattatgactactttcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccattgcaaatttaacagcttctg	52	52	17
HPV10 7722 YML001W caccaacttattatgactactttcaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccattgcaaatttaacagcttctgg	53	52	17
HPV10 7767 YML001W cgttttctaggttgccttgccaataGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctttcacataattactgttctggct	52	57	15
HPV10 7769 YML001W ttttctaggttgccttgccaataaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttcacataattactgttctggctgc	53	53	17
HPV10 7777 YML001W gttgccttgccaataaaatgtgcttGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattactgttctggctgcgttttcta	53	55	17
HPV10 7778 YML001W ttgccttgccaataaaatgtgcttcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttactgttctggctgcgttttctag	55	53	17
HPV10 7781 YML001W ccttgccaataaaatgtgcttccaaGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgttctggctgcgttttctaggtt	57	55	17
HPV10 7786 YML001W ccaataaaatgtgcttccaaatctcGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctggctgcgttttctaggttgcctt	58	52	15
HPV10 7799 YML001W cttccaaatctccaccaagacacacGTACGTGGAGATCGACATAA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctaggttgccttgccaataaaatgt	53	57	15
HPV11 636 YBL072C cacaacctttaacacaacattaccaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtggacaaggtggacaaacaagac	58	53	17

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HPV11	1678	YBL072C	gcacgtacattaggtacgttattaaTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagtaaataagagcagatgtaccgt				52	53	17
HPV11	1679	YBL072C	cacgtacattaggtacgttattaaaTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtaaataagagcagatgtaccgtg				53	52	17
HPV11	1760	YBL072C	ccctgtattggtttaggacaggcatTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctaaaatacaaagtggcgtacga				53	58	17
HPV11	1771	YBL072C	tttaggacaggcatttcaaatgcaaTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaagtggcgtacgagccctgtattg				58	53	15
HPV11	1776	YBL072C	gacaggcatttcaaatgcaagtacaTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcgtacgagccctgtattggttta				58	55	15
HPV11	1777	YBL072C	acaggcatttcaaatgcaagtacagTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcgtacgagccctgtattggtttag				58	53	15
HPV11	1781	YBL072C	gcatttcaaatgcaagtacagttatTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacgagccctgtattggtttaggaca				57	52	15
HPV11	3002	YBL072C	ctaacaccacccaaacggtgctttaTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacaggacaccagttatgaaatgtg				53	58	15
HPV11	3019	YBL072C	gtgctttaaaaaacagggaaatactTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaatgtggctaacaccacccaaac				57	52	15
HPV11	3072	YBL072C	acaatgtaatggagtatgtggtatgTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaggtaaaatttgatggctgtgaa				53	52	15
HPV11	3097	YBL072C	gacacatatatacctgcaggacaacTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacaatgtaatggagtatgtggtat				52	55	17
HPV11	3098	YBL072C	acacatatatacctgcaggacaacgTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaatgtaatggagtatgtggtatg				52	55	17
HPV11	3113	YBL072C	caggacaacgactcatgggtaaaagTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgtggtatggacacatatatacct				52	57	17
HPV11	3116	YBL072C	gacaacgactcatgggtaaaagtaaTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtatggacacatatatacctgca				53	55	17
HPV11	3117	YBL072C	acaacgactcatgggtaaaagtaacTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtatggacacatatatacctgcag				55	53	17
HPV11	3123	YBL072C	actcatgggtaaaagtaactagttcTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacacatatatacctgcaggacaac				55	52	17
HPV11	3130	YBL072C	ggtaaaagtaactagttccgtagatTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatatacctgcaggacaacgactcat				55	53	17
HPV11	3131	YBL072C	gtaaaagtaactagttccgtagatgTTCGCCTGACTTGAAAGACG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatacctgcaggacaacgactcatg				57	52	17

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HPV11 3132 YBL072C taaaagtaactagttccgtagatgcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatacctgcaggacaacgactcatgg	58	52	17
HPV11 3138 YBL072C taactagttccgtagatgccaagggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcaggacaacgactcatgggtaaaa	57	57	17
HPV11 3145 YBL072C ttccgtagatgccaagggcatatatTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacgactcatgggtaaaagtaacta	52	57	15
HPV11 3150 YBL072C tagatgccaagggcatatattatacTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctcatgggtaaaagtaactagttcc	53	52	17
HPV11 3153 YBL072C atgccaagggcatatattatacatgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgggtaaaagtaactagttccgta	52	52	17
HPV11 3156 YBL072C ccaagggcatatattatacatgtggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtaaaagtaactagttccgtagat	52	53	17
HPV11 3161 YBL072C ggcatatattatacatgtggacaatTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagtaactagttccgtagatgccaa	53	52	17
HPV11 3453 YBL072C ccaacatcagatccgtggacagtacTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtccactaacaacaccctgtgtgtg	58	58	15
HPV11 3463 YBL072C atccgtggacagtacaatcaacaacTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacaccctgtgtgtggccaacatca	58	55	15
HPV11 3470 YBL072C gacagtacaatcaacaacatcgtcaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgtgtggccaacatcagatccgt	58	55	17
HPV11 3492 YBL072C tcactgacaattacaacaagcaccaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgtggacagtacaatcaacaacatc	55	55	15
HPV11 3498 YBL072C acaattacaacaagcaccaaagaagTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagtacaatcaacaacatcgtcact	53	52	17
HPV11 3512 YBL072C caccaaagaaggaacaactgtcacaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacatcgtcactgacaattacaacaa	52	57	21
HPV11 3520 YBL072C aaggaacaactgtcacagtgcagctTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactgacaattacaacaagcaccaaa	52	58	15
HPV11 3523 YBL072C gaacaactgtcacagtgcagctacgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacaattacaacaagcaccaaagaa	52	58	15
HPV11 3524 YBL072C aacaactgtcacagtgcagctacgcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaattacaacaagcaccaaagaag	52	58	15
HPV11 3532 YBL072C tcacagtgcagctacgcctatagtgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacaagcaccaaagaaggaacaact	53	58	15
HPV11 3538 YBL072C tgcagctacgcctatagtgcaactgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaccaaagaaggaacaactgtcaca	55	58	15

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HPV11	3548	YBL072C	cctatagtgcaactgcaaggtgattTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaacaactgtcacagtgcagctac	58	57	17
HPV11	3555	YBL072C	tgcaactgcaaggtgattccaattgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgtcacagtgcagctacgcctata	58	55	15
HPV11	3657	YBL072C	cctcacctgaggcaccacataaaaaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattagcatcttcaacgtggcattgg	55	58	15
HPV11	3690	YBL072C	taacattaacatatagcagtgaggaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgaggcaccacataaaaatgcaatt	52	52	17
HPV11	3851	YBL072C	tagtgcctgtacaaattgctgcagcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtacataacatacgtgtatggag	53	57	15
HPV11	3854	YBL072C	tgcctgtacaaattgctgcagcaacTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacataacatacgtgtatggaggta	52	57	15
HPV11	3856	YBL072C	cctgtacaaattgctgcagcaacaaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcataacatacgtgtatggaggtagt	53	57	15
HPV11	4123	YBL072C	tgatgttaacctgtcacttaaatgaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacattgtgcaaacgcaacaataatg	52	52	17
HPV11	4128	YBL072C	ttaacctgtcacttaaatgatggtgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgcaaacgcaacaataatggtgat	53	52	17
HPV11	4136	YBL072C	tcacttaaatgatggtgatacatggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcaacaataatggtgatgttaacct	52	52	15
HPV11	4147	YBL072C	atggtgatacatggttgtttctgtgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtgatgttaacctgtcacttaaat	52	53	17
HPV11	4183	YBL072C	catttgttgtagctgtacttggattTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatggttgtttctgtggttgtttact	52	53	17
HPV11	4204	YBL072C	gattgttgttactacattacagggcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtactgcatttgttgtagctgtactt	52	53	17
HPV11	4205	YBL072C	attgttgttactacattacagggctTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactgcatttgttgtagctgtacttg	53	53	17
HPV11	4288	YBL072C	tggattatgtgtatatgtcacatggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtaaatcaaaccgcaatactact	52	52	17
HPV11	4290	YBL072C	gattatgtgtatatgtcacatggtgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtaaatcaaaccgcaatactactgt	52	52	17
HPV11	4291	YBL072C	attatgtgtatatgtcacatggtgaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaatcaaaccgcaatactactgtg	52	52	19
HPV11	4322	YBL072C	agattatgtgtacatgaactagagtTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtatatgtcacatggtgataatg	52	52	17

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HPV11 4413 YBL072C taaacgtgcgtcagccacacaactaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCataatgaaacctagggcacgcagac	57	58	19
HPV11 4419 YBL072C tgcgtcagccacacaactatatcaaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaacctagggcacgcagacgtaaac	58	57	19
HPV11 4467 YBL072C tcccccagatgtaattcctaaagttTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaaacatgcaaggccactggtacat	57	55	15
HPV11 4721 YBL072C ctattattaatgctggtgcacctgaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcattgtgtccttaattgaggagtct	53	55	17
HPV11 4864 YBL072C tttacagaaccgtctgtaatacagcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccactagtgtgtttcaaaatcccct	55	53	19
HPV11 4904 YBL072C aggccagtggtcacatacttatatcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtaatacagccccaaccacctgtg	58	55	17
HPV11 4906 YBL072C gccagtggtcacatacttatatctgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaatacagccccaaccacctgtgga	58	55	17
HPV11 4931 YBL072C ccccaacaataacatcccaacatgtTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggccagtggtcacatacttatatct	55	57	17
HPV11 4973 YBL072C acacttttgttgtatcctctagtgaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccaacatgtagaagacattccacta	53	53	15
HPV11 4982 YBL072C ttgtatcctctagtgatagtggaccTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaagacattccactagacactttt	52	55	17
HPV11 4985 YBL072C tatcctctagtgatagtggacctacTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagacattccactagacacttttgtt	52	55	17
HPV11 4997 YBL072C atagtggacctacatccagtactccTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagacacttttgttgtatcctctagt	52	57	17
HPV11 5004 YBL072C acctacatccagtactcctcttcctTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttgttgtatcctctagtgatagtg	52	58	19
HPV11 5016 YBL072C tactcctcttcctcgtgcttttcctTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctagtgatagtggacctacatcca	55	58	15
HPV11 5125 YBL072C gtaacttatgacaaccctgtctatgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgtttttgtccacgccacagcgatt	58	53	17
HPV11 5126 YBL072C taacttatgacaaccctgtctatgaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtttttgtccacgccacagcgattg	58	53	17
HPV11 5135 YBL072C acaaccctgtctatgaaggagaagaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacgccacagcgattggtaacttat	57	57	17
HPV11 5144 YBL072C tctatgaaggagaagatgtaagtttTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcgattggtaacttatgacaaccct	55	52	17

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HPV11 5259 YBL072C gggtcttgtgcgttttagtcgcattTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatagaccagctataacgtccagac	57	58	17
HPV11 5260 YBL072C ggtcttgtgcgttttagtcgcattgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatagaccagctataacgtccagacg	57	57	15
HPV11 5261 YBL072C gtcttgtgcgttttagtcgcattggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagaccagctataacgtccagacgg	58	57	15
HPV11 5267 YBL072C tgcgttttagtcgcattgggcaacgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagctataacgtccagacggggtctt	58	58	13
HPV11 5328 YBL072C tgcccgcatacattattttcaggacTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacacacgcagtggacaacatatag	55	55	15
HPV11 5330 YBL072C cccgcatacattattttcaggacatTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacacgcagtggacaacatataggt	57	55	15
HPV11 5350 YBL072C gacatttcaccagttacacaagctgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaggtgcccgcatacattattttca	53	55	15
HPV11 5351 YBL072C acatttcaccagttacacaagctgcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggtgcccgcatacattattttcag	55	55	15
HPV11 5372 YBL072C ctgcagaggaaatagaactgcacccTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaggacatttcaccagttacacaa	53	58	15
HPV11 5380 YBL072C gaaatagaactgcaccctctagtggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttcaccagttacacaagctgcaga	55	57	15
HPV11 5381 YBL072C aaatagaactgcaccctctagtggcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttcaccagttacacaagctgcagag	57	57	15
HPV11 5402 YBL072C tggctgcagaaaatgacacgtttgaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaggaaatagaactgcaccctcta	55	57	17
HPV11 5405 YBL072C ctgcagaaaatgacacgtttgatatTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaaatagaactgcaccctctagtg	57	53	17
HPV11 5417 YBL072C acacgtttgatatttatgctgaaccTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcaccctctagtggctgcagaaaat	58	52	17
HPV11 5526 YBL072C gggtaataccacagtcccattgtcaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacacctaataccctttcacaatcgt	53	58	19
HPV11 5527 YBL072C ggtaataccacagtcccattgtcaaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacctaataccctttcacaatcgtg	55	57	19
HPV11 5528 YBL072C gtaataccacagtcccattgtcaatTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacctaataccctttcacaatcgtgg	55	55	19
HPV11 5540 YBL072C tcccattgtcaatccctagtgactgTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttcacaatcgtggggtaataccaca	55	57	15

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HPV11 5548 YBL072C tcaatccctagtgactggtttgtgcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgtggggtaataccacagtcccatt	58	57	15
HPV11 5570 YBL072C tgcagtctgggcctgacataactttTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattgtcaatccctagtgactggttt	53	58	17
HPV11 5575 YBL072C tctgggcctgacataacttttcctaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaatccctagtgactggtttgtgca	57	57	15
HPV11 5651 YBL072C gccctgtttttattacaggttctgaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctgtaactcctgctttacctaca	55	55	15
HPV11 5652 YBL072C ccctgtttttattacaggttctgacTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctgtaactcctgctttacctacag	57	53	15
HPV11 5874 YBL072C tgggacatccatattactctatcaaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgccagcagttctagactccttgct	58	53	15
HPV11 5876 YBL072C ggacatccatattactctatcaaaaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccagcagttctagactccttgctgt	58	52	15
HPV11 5981 YBL072C tttgcattacctgattcatccctgtTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggtagtgttgccagatcctaacaa	55	55	21
HPV11 5994 YBL072C attcatccctgtttgaccccactacTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagatcctaacaagtttgcattacct	52	57	15
HPV11 6137 YBL072C tatggtggtaatcctggtcaggataTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgatgatgtagaaaatagtggtgg	52	57	17
HPV11 6141 YBL072C gtggtaatcctggtcaggataatagTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgtagaaaatagtggtgggtat	52	55	19
HPV11 6142 YBL072C tggtaatcctggtcaggataataggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgtagaaaatagtggtgggtatg	53	55	19
HPV11 6144 YBL072C gtaatcctggtcaggataatagggtTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtagaaaatagtggtgggtatggt	53	57	19
HPV11 6145 YBL072C taatcctggtcaggataatagggttTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtagaaaatagtggtgggtatggtg	55	55	19
HPV11 6174 YBL072C taggtatggattataaacaaacccaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctggtcaggataatagggttaat	53	52	17
HPV11 6177 YBL072C gtatggattataaacaaacccagctTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtcaggataatagggttaatgta	52	53	17
HPV11 6178 YBL072C tatggattataaacaaacccagctaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtcaggataatagggttaatgtag	53	52	17
HPV11 6241 YBL072C gggtaagggtacacaatgttcaaatTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgctccaccgttaggtgaacatt	57	55	19

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HPV11	6299	YBL072C	gaacttattaccagtgttatacaggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacaaaatggtgactgccccccgtt	58	52	19
HPV11	6313	YBL072C	tgttatacaggatggggacatggttTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgccccccgttggaacttattacca	58	57	13
HPV11	6453	YBL072C	acccttatggtgataggttgtttttTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctgattatttgcaaatggctgca	53	53	19
HPV11	6572	YBL072C	ggtaataacagatcatctgtagctaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcctgatgacctgttggtaaaagg	57	53	13
HPV11	6574	YBL072C	taataacagatcatctgtagctagtTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctgatgacctgttggtaaaagggg	58	52	15
HPV11	6686	YBL072C	ggacataacaatggtatttgctgggTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaccatattggcttcaaaaggctca	53	55	15
HPV11	6831	YBL072C	tggaggagtttgatttacagtttatTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagattataaggaatacatgcgccat	52	52	17
HPV11	6891	YBL072C	tcatggcctatatacacacaatgaaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtagcattacattatctgcagaa	52	53	17
HPV11	6896	YBL072C	gcctatatacacacaatgaatccttTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcattacattatctgcagaagtcat	52	53	15
HPV11	6914	YBL072C	aatccttctgttttggaggactggaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagtcatggcctatatacacacaat	52	57	19
HPV11	6946	YBL072C	tttatcgcctccaccaaatggtacaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctgttttggaggactggaactttg	55	57	17
HPV11	6966	YBL072C	gtacactggaggatacttatagataTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctttggtttatcgcctccaccaaat	55	53	17
HPV11	6967	YBL072C	tacactggaggatacttatagatatTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttggtttatcgcctccaccaaatg	55	52	15
HPV11	6974	YBL072C	gaggatacttatagatatgtacagtTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatcgcctccaccaaatggtacact	57	52	15
HPV11	7015	YBL072C	tcagaaacccacacctgaaaaagaaTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatgtacagtcacaggccattacct	55	55	15
HPV11	7162	YBL072C	gacgtctgctcgtacaggtataaagTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttattgcaaagtggatatcgaggac	53	57	13
HPV11	7163	YBL072C	acgtctgctcgtacaggtataaagcTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtattgcaaagtggatatcgaggacg	55	57	13
HPV11	7166	YBL072C	tctgctcgtacaggtataaagcgccTTCGCCTGACTTGAAAGACG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcaaagtggatatcgaggacggac	58	58	13

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HPV11	7466	YBL072C	tgactaagttgtgttttgcacgcgcTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtattatgtgtgtcctgttacaccca				53	57	19	
HPV11	7468	YBL072C	actaagttgtgttttgcacgcgccgTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttatgtgtgtcctgttacacccagt				55	58	17	
HPV11	7477	YBL072C	tgttttgcacgcgccgtttgtgttgTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctgttacacccagtgactaagtt				55	58	15	
HPV11	7488	YBL072C	cgccgtttgtgttgccttcatattaTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccagtgactaagttgtgttttgcac				55	57	15	
HPV11	7490	YBL072C	ccgtttgtgttgccttcatattataTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtgactaagttgtgttttgcacgc				55	53	15	
HPV11	7648	YBL072C	gtacatattgccctgccaagtatctTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactaatcccatatgttgtgtgccaa				53	57	17	
HPV11	7649	YBL072C	tacatattgccctgccaagtatcttTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctaatcccatatgttgtgtgccaag				55	55	17	
HPV11	7668	YBL072C	tatcttgccaacaacacacctggccTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccaaggtacatattgccctgccaa				58	58	17	
HPV11	7735	YBL072C	tttgtacaatgttgtggattgcagcTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgactaatgtacaataaacctgtcg				52	53	15	
HPV11	7746	YBL072C	ttgtggattgcagccaaaggttaaaTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaataaacctgtcggtttgtacaat				52	55	17	
HPV11	7751	YBL072C	gattgcagccaaaggttaaaagcatTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacctgtcggtttgtacaatgttgt				53	55	17	
HPV11	7752	YBL072C	attgcagccaaaggttaaaagcattTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacctgtcggtttgtacaatgttgtg				55	53	17	
HPV11	7759	YBL072C	ccaaaggttaaaagcatttttggctTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtttgtacaatgttgtggattgca				53	53	15	
HPV11	7765	YBL072C	gttaaaagcatttttggcttctagcTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacaatgttgtggattgcagccaaa				53	52	15	
HPV11	7766	YBL072C	ttaaaagcatttttggcttctagctTTCGCCTGACTTGAAAGACG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaatgttgtggattgcagccaaag				55	52	15	
HPV12	161	YDR286C	tgattgggacaaatggcacagcaggTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtataaggcttggttcttttgcaat				52	58	17	
HPV12	459	YDR286C	atatagagcttgctactggaaaatcTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttatcaacaaacagtgctaggtaga				52	52	17	
HPV12	465	YDR286C	agcttgctactggaaaatctatattTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaaacagtgctaggtagagatata				52	52	17	

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HPV12	632	YDR286C	aataatgatcggtaaagaggtcaccTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagacagtgcaagcatttgtatct				55	53	15	
HPV12	658	YDR286C	tgcaagattttaccttggagcttagTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaataatgatcggtaaagaggtcacc				53	53	21	
HPV12	660	YDR286C	caagattttaccttggagcttagtgTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaatgatcggtaaagaggtcaccgt				55	53	21	
HPV12	664	YDR286C	attttaccttggagcttagtgagctTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatcggtaaagaggtcaccgtgcaa				58	55	17	
HPV12	687	YDR286C	ctgcagcctgaagtgttaccagttgTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagattttaccttggagcttagtga				52	58	15	
HPV12	690	YDR286C	cagcctgaagtgttaccagttgaccTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattttaccttggagcttagtgagct				53	58	15	
HPV12	717	YDR286C	ctttgtgaagaggaattaccaaacgTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagcctgaagtgttaccagttgacct				57	53	17	
HPV12	722	YDR286C	tgaagaggaattaccaaacgagcagTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaagtgttaccagttgacctgcttt				55	55	17	
HPV12	748	YDR286C	aaacggaggaggagtcagatatcgaTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgaagaggaattaccaaacgagcag				55	58	19	
HPV12	754	YDR286C	aggaggagtcagatatcgacaggacTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaattaccaaacgagcaggaaacg				57	58	19	
HPV12	756	YDR286C	gaggagtcagatatcgacaggactgTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaattaccaaacgagcaggaaacgga				55	58	17	
HPV12	772	YDR286C	acaggactgtattcaaaatcattgcTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaaacggaggaggagtcagatatc				58	52	13	
HPV12	776	YDR286C	gactgtattcaaaatcattgcaccgTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacggaggaggagtcagatatcgaca				58	53	13	
HPV12	781	YDR286C	tattcaaaatcattgcaccgtgtggTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaggagtcagatatcgacaggact				58	53	13	
HPV12	812	YDR286C	ctcctgtgaggtcaaccttcgtattTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaaatcattgcaccgtgtggctgca				57	58	15	
HPV12	841	YDR286C	tcaacgcaactgatactggcattagTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgtgaggtcaaccttcgtattttt				53	55	21	
HPV12	847	YDR286C	caactgatactggcattaggaccctTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtcaaccttcgtatttttgtcaac				53	58	17	
HPV12	1385	YDR286C	attatctgtcattgctgcgtagtagTCTTCCTCAGCCGTGGAGTT				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggaggatcaggggccatagatatt				58	53	15	

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HPV12 1393 YDR286C tcattgctgcgtagtagcaatattaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaggggccatagatattgattatct	53	53	13
HPV12 1404 YDR286C tagtagcaatattaaagccacgttaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatattgattatctgtcattgctgc	52	52	17
HPV12 1964 YDR286C cagtagcatggctagcacataatcaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaagcttgcaccagaagatagcaat	55	57	19
HPV12 3054 YDR286C ataaggagccagaaaatgcaaatgtTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccagtgcctgtggaggtcatttat	57	53	17
HPV12 3059 YDR286C gagccagaaaatgcaaatgtgtataTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcctgtggaggtcatttatgataa	53	53	17
HPV12 3060 YDR286C agccagaaaatgcaaatgtgtatacTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcctgtggaggtcatttatgataag	55	52	17
HPV12 3062 YDR286C ccagaaaatgcaaatgtgtatacaaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgtggaggtcatttatgataagga	53	52	17
HPV12 3078 YDR286C tgtatacaatgtggaagtatgtgtaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgataaggagccagaaaatgcaaat	52	52	17
HPV12 3117 YDR286C aggatgtatggcataaaaccacaagTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaagtatgtgtattatatggaccca	52	53	17
HPV12 3120 YDR286C atgtatggcataaaaccacaagtggTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtatgtgtattatatggacccagag	53	53	17
HPV12 3123 YDR286C tatggcataaaaccacaagtggtgtTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgtattatatggacccagaggat	53	55	17
HPV12 3127 YDR286C gcataaaaccacaagtggtgtaaatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtattatatggacccagaggatgtat	52	53	17
HPV12 3128 YDR286C cataaaaccacaagtggtgtaaatcTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattatatggacccagaggatgtatg	53	52	17
HPV12 3142 YDR286C tggtgtaaatcagacgggcatttacTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaggatgtatggcataaaaccacaa	53	55	15
HPV12 3144 YDR286C gtgtaaatcagacgggcatttactaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggatgtatggcataaaaccacaagt	53	55	15
HPV12 3145 YDR286C tgtaaatcagacgggcatttactatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgtatggcataaaaccacaagtg	53	53	15
HPV12 3147 YDR286C taaatcagacgggcatttactatttTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtatggcataaaaccacaagtggt	53	52	15
HPV12 3158 YDR286C ggcatttactatttacatggagactTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaaccacaagtggtgtaaatcagac	53	53	17

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HPV12 3159 YDR286C gcatttactatttacatggagacttTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaccacaagtggtgtaaatcagacg	55	52	17
HPV12 3224 YDR286C tatagtaaaactggacaatgggaagTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacttttttgctgatggtgcacgaat	53	52	19
HPV12 3229 YDR286C taaaactggacaatgggaagttaagTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttgctgatggtgcacgaatgtata	53	52	19
HPV12 3237 YDR286C gacaatgggaagttaaggttaataaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtgcacgaatgtatagtaaaact	52	52	19
HPV12 3254 YDR286C gttaataaggaaactgtgtttgctcTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtaaaactggacaatgggaagttaa	52	52	15
HPV12 3456 YDR286C aaacgcagcaaaggcgatcaaggtcTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccatctagcagaacaaggcgacag	58	58	21
HPV12 4122 YDR286C tgaaatatccgaagggagttgaaacTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcagagaaaggattttgatgagact	52	53	17
HPV12 4124 YDR286C aaatatccgaagggagttgaaactgTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagagaaaggattttgatgagactgt	52	53	17
HPV12 4136 YDR286C ggagttgaaactgcatatggcaactTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgatgagactgtgaaatatccgaa	52	57	13
HPV12 4137 YDR286C gagttgaaactgcatatggcaacttTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgagactgtgaaatatccgaag	53	55	13
HPV12 4138 YDR286C agttgaaactgcatatggcaacttaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgagactgtgaaatatccgaagg	55	53	13
HPV12 4140 YDR286C ttgaaactgcatatggcaacttagaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgagactgtgaaatatccgaaggga	55	53	15
HPV12 4143 YDR286C aaactgcatatggcaacttagacagTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgactgtgaaatatccgaagggagtt	55	53	15
HPV12 4149 YDR286C catatggcaacttagacagcctataTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaatatccgaagggagttgaaact	53	55	15
HPV12 4156 YDR286C caacttagacagcctataacataacTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccgaagggagttgaaactgcatatg	57	52	15
HPV12 4529 YDR286C aatctgtgggtccagcagatatattTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggttgtaaggccttcacttgttcct	57	55	17
HPV12 4535 YDR286C tgggtccagcagatatattaccaatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaggccttcacttgttcctgaatct	55	55	15
HPV12 4537 YDR286C ggtccagcagatatattaccaatagTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggccttcacttgttcctgaatctgt	57	53	17

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HPV12	4538	YDR286C	gtccagcagatatattaccaatagaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccttcacttgttcctgaatctgtg				57	53 17
HPV12	4613	YDR286C	aatcctcagcaactgatctacttccTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcttcctcggtagttccattaact				55	55 17
HPV12	4622	YDR286C	caactgatctacttccaggagaagtTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtagttccattaactgaatcctca				53	57 19
HPV12	4640	YDR286C	gagaagttgagacaatagctgagatTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcctcagcaactgatctacttcca				55	55 15
HPV12	4641	YDR286C	agaagttgagacaatagctgagattTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctcagcaactgatctacttccag				57	53 15
HPV12	4643	YDR286C	aagttgagacaatagctgagattaaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctcagcaactgatctacttccagga				57	52 15
HPV12	4646	YDR286C	ttgagacaatagctgagattaatccTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagcaactgatctacttccaggagaa				55	52 17
HPV12	4649	YDR286C	agacaatagctgagattaatcctgtTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaactgatctacttccaggagaagtt				53	53 17
HPV12	4651	YDR286C	acaatagctgagattaatcctgtttTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgatctacttccaggagaagttga				55	52 17
HPV12	4658	YDR286C	ctgagattaatcctgtttcagagggTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacttccaggagaagttgagacaata				53	55 17
HPV12	4661	YDR286C	agattaatcctgtttcagagggcccTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccaggagaagttgagacaatagct				55	57 17
HPV12	4663	YDR286C	attaatcctgtttcagagggccctaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaggagaagttgagacaatagctga				55	57 17
HPV12	4673	YDR286C	tttcagagggccctacgattgattcTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgagacaatagctgagattaatcct				52	57 19
HPV12	4703	YDR286C	ttgtgacaacaagcagaggctccagTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagagggccctacgattgattcacct				58	58 15
HPV12	4728	YDR286C	tgcaatattggaagttgcaccagacTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttgtgacaacaagcagaggctcca				58	55 17
HPV12	4730	YDR286C	caatattggaagttgcaccagacccTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgacaacaagcagaggctccagt				58	57 17
HPV12	4739	YDR286C	aagttgcaccagaccctatacctccTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagcagaggctccagtgcaatattg				57	58 19
HPV12	4742	YDR286C	ttgcaccagaccctatacctccaacTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagaggctccagtgcaatattggaa				57	58 19

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HPV12	4751	YDR286C	accctatacctccaacacgtgttagTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagtgcaatattggaagttgcacca				55	57 19
HPV12	4835	YDR286C	ctcaaggtgaaacatctttggcagaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaaattataacagagtccacacct				52	57 17
HPV12	4841	YDR286C	gtgaaacatctttggcagaccacatTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtataacagagtccacacctgctcaa				55	57 17
HPV12	4842	YDR286C	tgaaacatctttggcagaccacatcTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCataacagagtccacacctgctcaag				57	55 15
HPV12	4844	YDR286C	aaacatctttggcagaccacatcctTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacagagtccacacctgctcaaggt				58	57 15
HPV12	4901	YDR286C	gtagtgacataacagacattattgaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatctggctcaggaggtcaaactata				55	52 19
HPV12	5052	YDR286C	aaggctagtacaacaagtgcaagttTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgtagaggagtgtccctaacaaata				55	55 15
HPV12	5055	YDR286C	gctagtacaacaagtgcaagttgatTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaggagtgtccctaacaaatagaa				53	55 15
HPV12	5056	YDR286C	ctagtacaacaagtgcaagttgataTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaggagtgtccctaacaaatagaag				55	53 15
HPV12	5060	YDR286C	tacaacaagtgcaagttgataatccTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtgtccctaacaaatagaaggcta				53	52 17
HPV12	5261	YDR286C	gatatgttagggtcagtaggctaggTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacctcaatactctacaacacctgct				55	57 15
HPV12	5262	YDR286C	atatgttagggtcagtaggctaggcTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctcaatactctacaacacctgctg				57	57 15
HPV12	5426	YDR286C	tgcaaggcactgttgaaagtacattTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccaacattcaggtgatgcaaccata				55	55 19
HPV12	5432	YDR286C	gcactgttgaaagtacatttgtagaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttcaggtgatgcaaccatagtgcaa				55	53 19
HPV12	5433	YDR286C	cactgttgaaagtacatttgtagatTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaggtgatgcaaccatagtgcaag				57	52 19
HPV12	5445	YDR286C	tacatttgtagatatggacatagcgTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccatagtgcaaggcactgttgaaa				55	52 15
HPV12	5474	YDR286C	atcctttgtctgaaagtattgaggcTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatttgtagatatggacatagcggaa				52	53 17
HPV12	5522	YDR286C	atgaagctgtggaggattttagcggTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggctcattctgatgacctattactt				53	57 19

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HPV12	5531	YDR286C	tggaggattttagcgggtcacaattTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgacctattacttgatgaagct				52	57	15
HPV12	5544	YDR286C	cgggtcacaattagttattggaaacTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttgatgaagctgtggaggatttta				53	53	17
HPV12	5546	YDR286C	ggtcacaattagttattggaaacagTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgaagctgtggaggattttagc				55	52	17
HPV12	5547	YDR286C	gtcacaattagttattggaaacagaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgaagctgtggaggattttagcg				57	52	17
HPV12	5601	YDR286C	ttttgaaactacaaggagcagttctTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagcacaacatcatacactgtgcccc				58	53	17
HPV12	5616	YDR286C	gagcagttcttattatgtgcaagatTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactgtgccccgttttgaaactacaa				55	53	15
HPV12	5617	YDR286C	agcagttcttattatgtgcaagataTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgtgccccgttttgaaactacaag				57	52	15
HPV12	5619	YDR286C	cagttcttattatgtgcaagatacaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgccccgttttgaaactacaagga				57	52	17
HPV12	5639	YDR286C	atacacaaggttattatgtggcttaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaggagcagttcttattatgtgcaa				52	52	17
HPV12	5684	YDR286C	cagaaatcatttatccaacaccagaTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcttatcctgaacatagaaatact				52	53	19
HPV12	5773	YDR286C	cggaggcgcaagcgtaaaagaaaatTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgacttttatttacatcctagcct				52	58	15
HPV12	5775	YDR286C	gaggcgcaagcgtaaaagaaaatatTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacttttatttacatcctagcctgc				53	55	15
HPV12	5776	YDR286C	aggcgcaagcgtaaaagaaaatattTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacttttatttacatcctagcctgcg				53	53	15
HPV12	5778	YDR286C	gcgcaagcgtaaaagaaaatatttgTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttttatttacatcctagcctgcgga				53	52	15
HPV12	5779	YDR286C	cgcaagcgtaaaagaaaatatttgtTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttatttacatcctagcctgcggag				55	52	15
HPV12	5803	YDR286C	tgatttacttgcagatggctgtgtgTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcgcaagcgtaaaagaaaatattt				52	55	17
HPV12	6032	YDR286C	agtatttcgcctcaaattgccagatTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctaaagtgtcaggaaatcaacaca				53	55	17
HPV12	6034	YDR286C	tatttcgcctcaaattgccagatccTCTTCCTCAGCCGTGGAGTT		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaagtgtcaggaaatcaacacaga				52	55	17

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HPV12 6041 YDR286C cctcaaattgccagatccaaacagaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaggaaatcaacacagagtatttc	52	57	19
HPV12 6051 YDR286C ccagatccaaacagatttgctttagTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacacagagtatttcgcctcaaatt	52	53	19
HPV12 6065 YDR286C atttgctttagctgacatgtctgtaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgcctcaaattgccagatccaaaca	57	53	15
HPV12 6076 YDR286C ctgacatgtctgtatataatcctgaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccagatccaaacagatttgcttta	53	53	15
HPV12 6149 YDR286C tcagcctttaggcgttggaagtactTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcagaggattggaaataagtaggg	55	58	15
HPV12 6233 YDR286C cagtaaggatgatagacagaacacaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaaactcaaataactatgccacag	52	55	15
HPV12 6236 YDR286C taaggatgatagacagaacacatcaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaactcaaataactatgccacaggca	53	53	15
HPV12 6241 YDR286C atgatagacagaacacatcatttgaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaataactatgccacaggcagtaag	53	52	17
HPV12 6244 YDR286C atagacagaacacatcatttgatccTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaactatgccacaggcagtaaggat	55	52	17
HPV12 6248 YDR286C acagaacacatcatttgatcctaaaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatgccacaggcagtaaggatgata	55	52	17
HPV12 6312 YDR286C ggagaacactgggagaaagccttacTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttatagtgggctgtacaccttgtgt	55	58	17
HPV12 6313 YDR286C gagaacactgggagaaagccttaccTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatagtgggctgtacaccttgtgtg	57	58	17
HPV12 6314 YDR286C agaacactgggagaaagccttacccTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatagtgggctgtacaccttgtgtgg	58	58	17
HPV12 6371 YDR286C ccctcccatagagttaaagaacactTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgcaccagctgaaaatggtgttt	55	57	15
HPV12 6479 YDR286C ccttgacatagtgaatgaaacttgcTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgcaacaaaacagatctgatgtca	52	53	19
HPV12 6610 YDR286C gtaaaacaggtgatgacattcctgaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgccagacatttctttgtgagagga	55	55	17
HPV12 6619 YDR286C gtgatgacattcctgacgcacaaatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttctttgtgagaggaggtaaaaca	52	57	19
HPV12 6620 YDR286C tgatgacattcctgacgcacaaattTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttctttgtgagaggaggtaaaacag	53	55	19

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HPV12 6622 YDR286C atgacattcctgacgcacaaattgaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctttgtgagaggaggtaaaacaggt	55	55	17
HPV12 6625 YDR286C acattcctgacgcacaaattgatgaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgagaggaggtaaaacaggtgat	55	55	17
HPV12 6634 YDR286C acgcacaaattgatgatggcaatatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggtaaaacaggtgatgacattcct	53	53	17
HPV12 6637 YDR286C cacaaattgatgatggcaatatgaaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaaacaggtgatgacattcctgac	53	52	15
HPV12 6690 YDR286C gatcaatctcaaaaggatataggtaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcagtattacattcctggagctca	53	52	15
HPV12 6768 YDR286C ttgtttaataggcccttctggcttcTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgctcattagtttctagtgatgctca	53	55	15
HPV12 6788 YDR286C gcttcaaagagcacagggtcataatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgctcagttgtttaataggcccttct	55	57	15
HPV12 6789 YDR286C cttcaaagagcacagggtcataataTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctcagttgtttaataggcccttctg	55	55	15
HPV12 6818 YDR286C catcctgtgggctaatcagatgtttTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaaagagcacagggtcataataatg	53	57	17
HPV12 6827 YDR286C ggctaatcagatgtttgtcacagttTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagggtcataataatggcatcctgt	55	55	17
HPV12 6828 YDR286C gctaatcagatgtttgtcacagttgTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagggtcataataatggcatcctgtg	55	53	17
HPV12 6829 YDR286C ctaatcagatgtttgtcacagttgtTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggtcataataatggcatcctgtgg	57	53	17
HPV12 6840 YDR286C tttgtcacagttgtagacaatacacTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatggcatcctgtgggctaatcagat	57	52	15
HPV12 6850 YDR286C ttgtagacaatacacgaaacaccaaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgggctaatcagatgtttgtcaca	55	53	19
HPV12 7026 YDR286C ttagcacagataaatgcaatgaactTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtaaagttcctttaaaggcagaagt	52	52	19
HPV12 7111 YDR286C acacatacagatatatcgaatctctTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccaactcctgacaatcctattcat	55	52	15
HPV12 7145 YDR286C gtgccctgataaaaatcctccaaaaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagatatatcgaatctctggctacta	52	55	17
HPV12 7146 YDR286C tgccctgataaaaatcctccaaaagTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatatatcgaatctctggctactag	53	53	15

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HPV12 7189 YDR286C atggcttaagtttttggactgtagaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccaaaagaaaagccggacccttat	55	53	15
HPV12 7192 YDR286C gcttaagtttttggactgtagatatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaaagaaaagccggacccttatgat	53	52	15
HPV12 7205 YDR286C gactgtagatatgactgagagacttTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacccttatgatggcttaagttttt	52	55	17
HPV12 7224 YDR286C agactttctttagacctggatcagtTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtttttggactgtagatatgactga	52	55	15
HPV12 7226 YDR286C actttctttagacctggatcagtatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttttggactgtagatatgactgaga	52	53	15
HPV12 7344 YDR286C gggaccaaaagaaaacgcaaaaactTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatcaagctatagaagttccataag	52	55	17
HPV12 7345 YDR286C ggaccaaaagaaaacgcaaaaactaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcaagctatagaagttccataagg	52	53	17
HPV12 7346 YDR286C gaccaaaagaaaacgcaaaaactaaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaagctatagaagttccataaggg	53	52	17
HPV12 7485 YDR286C gtgagttggtgccaaattagtctcaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaacagaccgcgcccggtacataaa	58	57	17
HPV12 7505 YDR286C tctcactttgttgccagaacataccTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCataaaggtgagttggtgccaaatta	52	55	15
HPV12 7515 YDR286C ttgccagaacataccgtgttcgtccTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttggtgccaaattagtctcacttt	53	58	17
HPV12 7531 YDR286C tgttcgtcctaacatgctcggattaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctcactttgttgccagaacatacc	55	57	15
HPV12 7533 YDR286C ttcgtcctaacatgctcggattaggTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcactttgttgccagaacataccgt	55	57	13
HPV12 7537 YDR286C tcctaacatgctcggattaggtcgaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttgttgccagaacataccgtgttc	55	58	15
HPV12 7565 YDR286C ccaaaggacctttggtttgccaaatTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctaacatgctcggattaggtcgacc	58	57	15
HPV12 7602 YDR286C ctcagttctggcacatttgtggaccTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttggtttgccaaatagcttacagca	53	58	15
HPV12 7607 YDR286C ttctggcacatttgtggaccgataaTCTTCCTCAGCCGTGGAGTT ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgccaaatagcttacagcagctca	55	57	15
HPV13 327 YHL031C gatttgctgtaacagttgaagaagaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccagtttaggcattttgacttcgcg	57	53	21

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HPV13 328 YHL031C atttgctgtaacagttgaagaagacATCACCGAACCGCAGTTAAG-					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagtttaggcattttgacttcgcgg	57	52	21		
HPV13 333 YHL031C ctgtaacagttgaagaagacacaaaATCACCGAACCGCAGTTAAG-					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaggcattttgacttcgcgggattt	55	53	21		
HPV13 336 YHL031C taacagttgaagaagacacaaagcaATCACCGAACCGCAGTTAAG-					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcattttgacttcgcgggatttgct	57	53	19		
HPV13 342 YHL031C ttgaagaagacacaaagcagtcaatATCACCGAACCGCAGTTAAG-					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgacttcgcgggatttgctgtaaca	57	53	19		
HPV13 375 YHL031C tgctaattcgctgctatttatgccaATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagacacaaagcagtcaattttggat	52	55	21		
HPV13 1127 YHL031C tgatataagtcctcgattggacgctATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggacatgttgaacagtcagtggact	57	57	19		
HPV13 1129 YHL031C atataagtcctcgattggacgctatATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacatgttgaacagtcagtggactgt	55	55	19		
HPV13 1386 YHL031C cgggtgttagaactccttaaatgtaATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagatagaagagcacacagggaccac	58	55	17		
HPV13 1683 YHL031C cgaacactggcaacctttcttaataATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaataaaagtagatgcacagtggc	52	55	21		
HPV13 1685 YHL031C aacactggcaacctttcttaatattATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaataaaagtagatgcacagtggcgc	55	52	21		
HPV13 3004 YHL031C ctaacacccccaaaacgctgttttaATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacaagatacaagtcgtgaaatgtg	52	57	19		
HPV13 3021 YHL031C ctgttttaagaaacagggacaaactATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaatgtggctaacacccccaaaac	57	53	15		
HPV13 3024 YHL031C ttttaagaaacagggacaaactgtgATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgtggctaacacccccaaaacgct	58	52	15		
HPV13 3031 YHL031C aaacagggacaaactgtggaagtaaATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaacacccccaaaacgctgttttaa	53	55	15		
HPV13 3038 YHL031C gacaaactgtggaagtaaaatatgaATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcccaaaacgctgttttaagaaacag	53	52	21		
HPV13 3062 YHL031C actgtaatacagacaatagaatggaATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggacaaactgtggaagtaaaatat	52	52	17		
HPV13 3097 YHL031C tggacatacatatatgtgtttgacaATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagacaatagaatggattatgtgtc	52	52	15		
HPV13 3115 YHL031C tttgacacagataaatggacaaaggATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgtgtcgtggacatacatatatgt	52	52	15		

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HPV13 3119 YHL031C acacagataaatggacaaaggtgaaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtcgtggacatacatatatgtgttt	52	53	15
HPV13 3146 YHL031C gaatggtagattataaagggttgtaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacagataaatggacaaaggtgaaa	52	52	19
HPV13 3241 YHL031C ttacaatgggaagtatgtattggcaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggaggctaaaaaatatggggaaac	53	53	15
HPV13 3251 YHL031C aagtatgtattggcagcacagtcatATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaaatatggggaaacgttacaatgg	52	55	15
HPV13 3471 YHL031C cattgtgtgtgtcacagactacgacATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattggaaacccccagaacacacaaa	55	57	19
HPV13 3494 YHL031C acaccctggacagtgcaaacaacaaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagcattgtgtgtgtcacagactac	55	58	19
HPV13 3687 YHL031C gaccgcccctaataattcacaaaaaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgttagcatcatctacatggcatt	52	55	17
HPV13 3688 YHL031C accgcccctaataattcacaaaaacATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgttagcatcatctacatggcattg	53	53	17
HPV13 3692 YHL031C cccctaataattcacaaaaacatgcATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagcatcatctacatggcattggacc	57	52	21
HPV13 3942 YHL031C taattgcacttacagtgtgtgtagtATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaccagcaagtcattactgccactt	55	53	19
HPV13 3948 YHL031C cacttacagtgtgtgtagttagcatATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaagtcattactgccacttgtaatt	52	55	17
HPV13 4458 YHL031C cagataaaatattaaagtggggcagATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccaaaggttgaacaaaacactctt	52	52	15
HPV13 4755 YHL031C caatattggatgtgtctgttacaacATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaccacatctcaatcagccactcca	58	52	15
HPV13 4764 YHL031C atgtgtctgttacaacacaaaacacATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaatcagccactccagcaatattg	55	52	17
HPV13 4767 YHL031C tgtctgttacaacacaaaacactacATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcagccactccagcaatattggat	55	52	15
HPV13 4877 YHL031C tttatatcgccatctactatttcccATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttctattgaaagtggtgcacacgt	55	52	15
HPV13 4886 YHL031C ccatctactatttcccctcattctaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaagtggtgcacacgtgtttatatc	53	55	17
HPV13 5023 YHL031C ggccttacatcaagtacaggttactATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgtccacgtctaggcctttacagta	58	57	17

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HPV13	5024	YHL031C	gccttacatcaagtacaggttactgATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtccacgtctaggcctttacagtag	58	55	17
HPV13	5091	YHL031C	ataaccctacatatgaaggtgaagaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtcgccccaacgccttataaccttt	58	53	15
HPV13	5252	YHL031C	tctatgtatactcgaagcggcaagcATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtttagtagaattggtcagagggg	57	57	21
HPV13	5266	YHL031C	aagcggcaagcatataggtggaaggATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtcagaggggtctatgtatactc	58	58	19
HPV13	5272	YHL031C	caagcatataggtggaagggtccatATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggggtctatgtatactcgaagcg	58	58	19
HPV13	5276	YHL031C	catataggtggaagggtccatttctATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtctatgtatactcgaagcggcaa	57	57	21
HPV13	5364	YHL031C	ctgcacaggatcacagtggtttgttATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaatagaattacacccccttgtggct	55	58	15
HPV13	5421	YHL031C	tggctgtaaacacctctgggtcattATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttatgcagaacctgaccctgaccct	58	58	15
HPV13	5454	YHL031C	cctccacaccatttgcacaatcttcATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaacacctctgggtcattgtcttct	55	57	15
HPV13	5511	YHL031C	ttcctctttcactaccaggtgatatATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttccgccccatggggtaatactact	58	55	15
HPV13	5529	YHL031C	gtgatatatttatacagcctggtccATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtactactgttcctctttcactacca	53	53	15
HPV13	5532	YHL031C	atatatttatacagcctggtcctgaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtactgttcctctttcactaccaggt	55	53	17
HPV13	5606	YHL031C	cctgctttacctacaggtcctgtttATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagtaacgccttataatcctgttac	53	58	15
HPV13	5610	YHL031C	ctttacctacaggtcctgtttttatATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacgccttataatcctgttacgcct	55	53	17
HPV13	5622	YHL031C	gtcctgtttttattactgcttctggATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcctgttacgcctgctttacctaca	57	53	15
HPV13	5623	YHL031C	tcctgtttttattactgcttctggaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctgttacgcctgctttacctacag	58	53	15
HPV13	5686	YHL031C	ccgtaaacgtgtttccttgttttttATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctacatggtattttacacgcaaac	53	53	21
HPV13	5758	YHL031C	cccctgtatcaaaagtaattactacATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaacaaactatatgtgcctcctccc	57	52	17

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HPV13 6007 YHL031C cctgtacaggtttagaggttggtagATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctcaactagtcaacgcttagtgtgg	57	57	19
HPV13 6046 YHL031C gtgttggtattagtggtcatccattATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaggttggtaggggtcaaccctta	58	55	19
HPV13 6147 YHL031C gccatggactataaacaaacacagtATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctggtcaggataatagggttaatgt	53	55	15
HPV13 6148 YHL031C ccatggactataaacaaacacagttATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtcaggataatagggttaatgtg	53	53	15
HPV13 6230 YHL031C tactggtgtaaatgtacaacctggaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaacattggggacagggcaagcaat	58	55	17
HPV13 6235 YHL031C gtgtaaatgtacaacctggagattgATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttggggacagggcaagcaatgtact	58	53	17
HPV13 6253 YHL031C gagattgccctcctttagaattaatATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgtactggtgtaaatgtacaacct	52	53	19
HPV13 6254 YHL031C agattgccctcctttagaattaattATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtactggtgtaaatgtacaacctg	53	52	19
HPV13 6309 YHL031C gatacaggatttggagccatgaattATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtaattcaggatggtgacatggt	55	55	15
HPV13 6317 YHL031C atttggagccatgaattttgcggaaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaggatggtgacatggtggatacag	58	55	15
HPV13 6322 YHL031C gagccatgaattttgcggaattgcaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtgacatggtggatacaggattt	55	57	17
HPV13 6323 YHL031C agccatgaattttgcggaattgcaaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtgacatggtggatacaggatttg	57	55	17
HPV13 6325 YHL031C ccatgaattttgcggaattgcaatcATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgacatggtggatacaggatttgga	55	53	19
HPV13 6403 YHL031C actatttacaaatggctgcggatccATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgcacgtccacatgcaaatatcct	55	55	13
HPV13 6423 YHL031C gatccttatggagacagattattttATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcctgactatttacaaatggctgc	53	52	15
HPV13 6499 YHL031C gctctgttggtgaacaaatcccagcATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcaaggcatttctttaacagggca	55	58	15
HPV13 6500 YHL031C ctctgttggtgaacaaatcccagcaATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcaaggcatttctttaacagggcag	57	58	15
HPV13 6505 YHL031C ttggtgaacaaatcccagcagaattATCACCGAACCGCAGTTAAG ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcatttctttaacagggcaggctct -	57	55	15

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HPV13 6511 YHL031C aacaaatcccagcagaattatatgtATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctttaacagggcaggctctgttggt 58 52 15
HPV13 6648 YHL031C ggacacaataatggtatatgttgggATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaccttattggttacaaaaggccca 53 53 17
HPV13 6649 YHL031C gacacaataatggtatatgttggggATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccttattggttacaaaaggcccag 55 53 17
HPV13 6650 YHL031C acacaataatggtatatgttggggcATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccttattggttacaaaaggcccagg 57 53 19
HPV13 6915 YHL031C ctatctccccctcctaatggaacatATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaattctagaagactggaactttgg 53 58 15
HPV13 7020 YHL031C tatgcgggtcttagtttttgggaggATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacctgataaagaaaaacaggatcc 53 57 19
HPV13 7131 YHL031C tcccctattcgtgtaggtaggaaacATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtattacaaacaggcgttcagtctag 53 57 15
HPV13 7157 YHL031C tgctgcatctacatctactgccacaATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcccctattcgtgtaggtaggaaac 57 58 15
HPV13 7159 YHL031C ctgcatctacatctactgccacaccATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccctattcgtgtaggtaggaaacgt 57 58 17
HPV13 7162 YHL031C catctacatctactgccacacctacATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtattcgtgtaggtaggaaacgtgct 55 57 13
HPV13 7500 YHL031C ctattgtttctgcgaccgatttgttATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatattaagtgcaaccgatttcggtt 52 55 21
HPV13 7514 YHL031C accgatttgttgcagcacgctgtttATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgatttcggttgctattgtttctgc 55 58 17
HPV13 7523 YHL031C ttgcagcacgctgtttatataatctATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgctattgtttctgcgaccgattt 53 53 17
HPV13 7577 YHL031C cttgccaaaatcacccacacacctgATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctaccgcctgccaaaattatccacc 58 58 15
HPV13 7603 YHL031C cgttgctagggcgcggttatatataATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttgccaaaatcacccacacacctg 58 58 17
HPV13 7608 YHL031C ctagggcgcggttatatatatttacATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaaaatcacccacacacctggcgtt 58 53 17
HPV13 7725 YHL031C aaaggttttttggctaccagcactaATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttttgtacttactagccaatgcct 52 55 19
HPV13 7729 YHL031C gttttttggctaccagcactacattATCACCGAACCGCAGTTAAG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtacttactagccaatgcctgaaa 53 55 19

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HPV13 7730 YHL031C ttttttggctaccagcactacatttATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtacttactagccaatgcctgaaag	55	53	19		
HPV13 7738 YHL031C ctaccagcactacatttttgtacagATCACCGAACCGCAGTTAAG					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagccaatgcctgaaaggtttttg	53	53	19		
HPV14d 172 YIL167W gcgacaactgactcttcaacagacaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaaaaacagagaatgcagactcat	52	58	17		
HPV14d 223 YIL167W agtaactattgtgatagcacagaaaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgcagatgaaggtccttctcctaa	57	52	17		
HPV14d 225 YIL167W taactattgtgatagcacagaaaccGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagatgaaggtccttctcctaaga	57	52	19		
HPV14d 234 YIL167W tgatagcacagaaaccaaatcttctGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtccttctcctaagagtaactatt	53	53	17		
HPV14d 236 YIL167W atagcacagaaaccaaatcttctttGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccttctcctaagagtaactattgt	52	52	15		
HPV14d 623 YIL167W aatttgctcttagaaccttccagaaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcttcgcatctttataactgctaca	53	53	17		
HPV14d 646 YIL167W aacctgttatttgaacaactgcagcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagaatttgctcttagaaccttcca	53	53	17		
HPV14d 1623 YIL167W aagcaaatgcatttgatatgtctgtGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaactattgttggccatcaaagtaca	52	52	17		
HPV14d 1747 YIL167W gcttgcccataataatcaggccaggGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccagaagatagtaatgctgtggcct	57	58	19		
HPV14d 1748 YIL167W cttgcccataataatcaggccaggtGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagaagatagtaatgctgtggcctg	57	58	19		
HPV14d 3377 YIL167W acaaaaagaagtgtccagaatcacaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcggtaccgatcaagatccagatcca	58	53	15		
HPV14d 3635 YIL167W aaggttactggacgaagctctcgatGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagttcaagaaatacaggaagacttg	52	58	17		
HPV14d 3847 YIL167W attttgatcagactgttaagtacccGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctttttctcctttaaccagagaaga	52	52	15		
HPV14d 3887 YIL167W gtcgtttggctcatttgatagcctaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttaagtacccgaaaggagtggacc	58	57	21		
HPV14d 4314 YIL167W acaccttagatccagtggagcctacGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtccatcagatattatacctgtg	53	58	19		
HPV14d 4329 YIL167W tggagcctacgacctcttctattgtGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatacctgtggacaccttagatcca	55	58	15		

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HPV14d 4331 YIL167W gagcctacgacctcttctattgttcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacctgtggacaccttagatccagt	57	57	15		
HPV14d 4332 YIL167W agcctacgacctcttctattgttccGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacctgtggacaccttagatccagtg	58	57	15		
HPV14d 4340 YIL167W acctcttctattgttccactcacggGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaccttagatccagtggagcctac	58	57	15		
HPV14d 4364 YIL167W gattccacaggaccagacctttgcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgacctcttctattgttccactcac	57	58	17		
HPV14d 4365 YIL167W attccacaggaccagacctttgccGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacctcttctattgttccactcacg	57	58	15		
HPV14d 4465 YIL167W tacaggaggctccagtgctatattaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctactgacactcctgtcacaacta	57	57	17		
HPV14d 4471 YIL167W aggctccagtgctatattagaagtaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacactcctgtcacaactagtacag	57	55	17		
HPV14d 4473 YIL167W gctccagtgctatattagaagtagcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcactcctgtcacaactagtacagga	57	55	15		
HPV14d 4474 YIL167W ctccagtgctatattagaagtagcaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactcctgtcacaactagtacaggag	57	55	15		
HPV14d 4575 YIL167W aatccacccctaccacaggtgaaagGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaatccctcctttcaagtaattacc	52	58	15		
HPV14d 4593 YIL167W gtgaaagttcattagcagacaatatGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaattaccgaatccacccctaccaca	57	52	19		
HPV14d 4611 YIL167W acaatatattggttacctctggttcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaccacaggtgaaagttcattagca	53	52	17		
HPV14d 4632 YIL167W gttctgggggacaaactattggaggGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagcagacaatatattggttacctct	52	58	15		
HPV14d 4633 YIL167W ttctgggggacaaactattggaggcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagacaatatattggttacctctg	53	58	17		
HPV14d 4640 YIL167W ggacaaactattggaggcgctacacGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatatattggttacctctggttctgg	53	58	13		
HPV14d 4641 YIL167W gacaaactattggaggcgctacaccGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatattggttacctctggttctggg	55	58	15		
HPV14d 4642 YIL167W acaaactattggaggcgctacacctGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatattggttacctctggttctgggg	57	58	15		
HPV14d 4656 YIL167W gcgctacacctgaacttatagaactGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggttctgggggacaaactattgga	57	57	15		

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HPV14d 4657 YIL167W cgctacacctgaacttatagaacttGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggttctgggggacaaactattggag	58	55	15
HPV14d 4659 YIL167W ctacacctgaacttatagaacttcaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttctgggggacaaactattggaggc	58	53	17
HPV14d 4677 YIL167W aacttcaagagttaccatctagataGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggaggcgctacacctgaacttata	57	52	15
HPV14d 4735 YIL167W aagaactagtaccccattacaaaggGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaatcgaagaaccaacacccccta	57	53	21
HPV14d 4744 YIL167W taccccattacaaaggatacagacaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaccaacacccccctagaagaacta	57	55	17
HPV14d 4759 YIL167W gatacagacagctataagaaggaggGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaagaactagtaccccattacaaa	52	55	17
HPV14d 4770 YIL167W ctataagaaggaggggtgggcttacGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaccccattacaaaggatacagaca	53	58	17
HPV14d 4784 YIL167W ggtgggcttacaaataggcgcttagGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggatacagacagctataagaaggag	55	58	17
HPV14d 4785 YIL167W gtgggcttacaaataggcgcttagtGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatacagacagctataagaaggagg	55	58	17
HPV14d 4786 YIL167W tgggcttacaaataggcgcttagtcGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatacagacagctataagaaggaggg	55	57	17
HPV14d 4788 YIL167W ggcttacaaataggcgcttagtccaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacagacagctataagaaggaggggt	57	58	19
HPV14d 4789 YIL167W gcttacaaataggcgcttagtccaaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagacagctataagaaggaggggtg	58	57	19
HPV14d 4790 YIL167W cttacaaataggcgcttagtccaacGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagacagctataagaaggaggggtgg	58	55	19
HPV14d 4801 YIL167W gcgcttagtccaacaagtttctgtaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaaggaggggtgggcttacaaata	57	57	15
HPV14d 4802 YIL167W cgcttagtccaacaagtttctgtagGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaggaggggtgggcttacaaatag	58	55	15
HPV14d 4979 YIL167W ggtaggccccaatattcagaaactcGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgagattttctagatgttcaaaggct	52	57	17
HPV14d 4980 YIL167W gtaggccccaatattcagaaactccGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagattttctagatgttcaaaggctg	52	57	17
HPV14d 4984 YIL167W gccccaatattcagaaactccagcaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttctagatgttcaaaggctgggta	53	58	15

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HPV14d 4985 YIL167W ccccaatattcagaaactccagcagGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttctagatgttcaaaggctgggtag	55	57	15		
HPV14d 5010 YIL167W ggtatctccgagttagtcgtcttggGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccccaatattcagaaactccagca	57	58	15		
HPV14d 5064 YIL167W gagcacaaattgggtctcaagttcaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaggcggactatacgcactcgttct	58	57	19		
HPV14d 5076 YIL167W ggtctcaagttcatttttatagagaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacgcactcgttctggagcacaaatt	57	52	21		
HPV14d 5238 YIL167W attttagtgcacattctgatgacttGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtagatgaaaatccactttctgag	52	52	17		
HPV14d 5259 YIL167W acttgcttttagatgaagctaatgaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgaggattttagtgcacattctgat	52	52	21		
HPV14d 5307 YIL167W ttgtgggtaatcgacgctcaacatcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgaagactttagtggctctcaatta	52	57	15		
HPV14d 5310 YIL167W tgggtaatcgacgctcaacatcttcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagactttagtggctctcaattagtt	52	57	15		
HPV14d 5312 YIL167W ggtaatcgacgctcaacatcttcatGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactttagtggctctcaattagttgt	52	57	15		
HPV14d 5313 YIL167W gtaatcgacgctcaacatcttcataGTCGCCAACGAGTGACAACA					
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HPV14d 5314 YIL167W taatcgacgctcaacatcttcatatGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttagtggctctcaattagttgtgg	53	53	15		
HPV14d 5320 YIL167W acgctcaacatcttcatataccgtcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggctctcaattagttgtgggtaatc	55	55	15		
HPV14d 5323 YIL167W ctcaacatcttcatataccgtccctGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctcaattagttgtgggtaatcgac	53	57	15		
HPV14d 5343 YIL167W tccctcgttttgaaacaaccagatcGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcgacgctcaacatcttcatatacc	55	55	15		
HPV14d 5350 YIL167W ttttgaaacaaccagatctgggtcaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaacatcttcatataccgtccctc	55	55	15		
HPV14d 5365 YIL167W atctgggtcatattatgcacaggatGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccgtccctcgttttgaaacaacca	57	55	15		
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ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggttattatgtagcttatcctgag	52	52	15		
HPV14d 5434 YIL167W catggatattatttatcctaccccaGTCGCCAACGAGTGACAACA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcttatcctgaggatagggacatta	55	53	15		

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HPV14d 5438 YIL167W gatattatttatcctaccccagagtGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcctgaggatagggacattagcat	55	53	17
HPV14d 5460 YIL167W agttgcctgttgtcattattcacacGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatggatattatttatcctacccca	52	53	15
HPV14d 5462 YIL167W ttgcctgttgtcattattcacacatGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggatattatttatcctaccccaga	52	53	17
HPV14d 5592 YIL167W cagctagtggtaaggtttaccttccGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcttttacagatggcagtttggcaa	53	57	17
HPV14d 5599 YIL167W tggtaaggtttaccttccaccatctGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagatggcagtttggcaagcagcta	58	57	17
HPV14d 5601 YIL167W gtaaggtttaccttccaccatctacGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatggcagtttggcaagcagctagt	58	55	17
HPV14d 5602 YIL167W taaggtttaccttccaccatctacaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatggcagtttggcaagcagctagtg	58	55	17
HPV14d 5606 YIL167W gtttaccttccaccatctacaccagGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagtttggcaagcagctagtggtaa	57	57	17
HPV14d 5638 YIL167W ggtccaaagtacggacgaatatgtgGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttccaccatctacaccagttgcca	58	57	15
HPV14d 5639 YIL167W gtccaaagtacggacgaatatgtgcGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttccaccatctacaccagttgccag	58	57	15
HPV14d 5647 YIL167W tacggacgaatatgtgcaaaggactGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctacaccagttgccagggtccaaa	58	57	15
HPV14d 5763 YIL167W taccaaaagtatctggaaatcaacaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgacgtgcaaagtgctaagataaaa	52	52	17
HPV14d 5879 YIL167W gcatgcagaggtatagaaataggcaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatccagataaagaaagactggtttg	52	57	17
HPV14d 5880 YIL167W catgcagaggtatagaaataggcagGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccagataaagaaagactggtttgg	53	55	17
HPV14d 5889 YIL167W gtatagaaataggcagaggacaaccGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaaagactggtttgggcatgcaga	57	55	19
HPV14d 5890 YIL167W tatagaaataggcagaggacaacctGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaagactggtttgggcatgcagag	58	55	19
HPV14d 5895 YIL167W aaataggcagaggacaacctttaggGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactggtttgggcatgcagaggtata	57	55	19
HPV14d 6094 YIL167W ggccttgccatgtgtagaagataaaGTCGCCAACGAGTGACAACA ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccttgcatgggggaacattgggata	58	57	15

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HPV14d 6095 YIL167W gccttgccatgtgtagaagataaacGTCGCCAACGAGTGACAACA
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HPV14d 6106 YIL167W tgtagaagataaaccacccccctggtGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaacattgggatagggccttgccat 58 58 17
HPV14d 6129 YIL167W gttcttgccctccaattgaattaaaGTCGCCAACGAGTGACAACA
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HPV14d 6130 YIL167W ttcttgccctccaattgaattaaaaGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgtagaagataaaccacccccctg 57 52 19
HPV14d 6374 YIL167W ggtaagacaggagatgacataccagGTCGCCAACGAGTGACAACA
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HPV14d 6380 YIL167W acaggagatgacataccagcagcacGTCGCCAACGAGTGACAACA
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HPV14d 6402 YIL167W cacaagttgatgagggtagcctaaaGTCGCCAACGAGTGACAACA
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HPV14d 6562 YIL167W cgcacaaggccacaataatggtattGTCGCCAACGAGTGACAACA
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HPV14d 6564 YIL167W cacaaggccacaataatggtatttgGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaatagaccattttggttacagcgc 55 53 21
HPV14d 6849 YIL167W tacctgcaccagacaatcctattcaGTCGCCAACGAGTGACAACA
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HPV14d 6855 YIL167W caccagacaatcctattcatgatacGTCGCCAACGAGTGACAACA
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HPV14d 6905 YIL167W actaggtgtcctgataaaaatcctcGTCGCCAACGAGTGACAACA
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HPV14d 6910 YIL167W gtgtcctgataaaaatcctcctaaaGTCGCCAACGAGTGACAACA
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HPV14d 6911 YIL167W tgtcctgataaaaatcctcctaaagGTCGCCAACGAGTGACAACA
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HPV14d 6913 YIL167W tcctgataaaaatcctcctaaagaaGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatattgagtctgcagcgactaggt 55 52 15
HPV14d 7061 YIL167W accgttaacggtacaaaaacagtttGTCGCCAACGAGTGACAACA
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HPV14d 7083 YIL167W tttcgactaggggatccatcaagggGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcgaccgttaacggtacaaaaaca 53 58 17
HPV14d 7088 YIL167W actaggggatccatcaagggtattaGTCGCCAACGAGTGACAACA
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HPV14d   7093     YIL167W gggatccatcaagggtattaaacgaGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacggtacaaaaacagtttcgacta      52      57      21
HPV14d   7096     YIL167W atccatcaagggtattaaacgaaaaGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtacaaaaacagtttcgactaggg      55      52      19
HPV14d   7106     YIL167W ggtattaaacgaaaacgcaagaattGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagtttcgactaggggatccatcaa      57      52      17
HPV14d   7127     YIL167W aattagacattatcgatttcggtgcGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaagggtattaaacgaaaacgcaa      52      52      17
HPV14d   7219     YIL167W cgcccgatacataaaggtgccaaatGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcactctgactaagcaaatatgagcc      55      58      15
HPV14d   7235     YIL167W gtgccaaatgaggtgagttgtttgcGTCGCCAACGAGTGACAACA
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HPV14d   7236     YIL167W tgccaaatgaggtgagttgtttgccGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatgagccgcgcccgatacataaag      58      57      15
HPV14d   7245     YIL167W aggtgagttgtttgccagaagaggtGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgcccgatacataaaggtgccaaat      57      58      17
HPV14d   7247     YIL167W gtgagttgtttgccagaagaggtcaGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcccgatacataaaggtgccaaatga      55      58      17
HPV14d   7248     YIL167W tgagttgtttgccagaagaggtcagGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccgatacataaaggtgccaaatgag      55      57      17
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ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacataaaggtgccaaatgaggtga      53      58      15
HPV14d   7255     YIL167W tttgccagaagaggtcagagccaacGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCataaaggtgccaaatgaggtgagtt      53      58      15
HPV14d   7263     YIL167W aagaggtcagagccaactcaggtttGTCGCCAACGAGTGACAACA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccaaatgaggtgagttgtttgcca      57      58      15
HPV14d   7351     YIL167W actcaaggaaatgtaagtgtgccagGTCGCCAACGAGTGACAACA
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ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgactcaaggaaatgtaagtgtgcca      55      52      15
HPV14d   7385     YIL167W ttcgaatttggcaaagttgaagaccGTCGCCAACGAGTGACAACA
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ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtaacttggcagaacattttcttg      52      57      15
HPV15    5        YLR373C acagcaccgataacggtaagattatCGTTTGAAGGCGCGACACAA
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HPV15    25      YLR373C  attatatctttgaaccgtaggcggtCGTTTGAAGGCGCGACACAA
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HPV15    48      YLR373C  gttctttctgattggtttggctgatCGTTTGAAGGCGCGACACAA
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HPV15    58      YLR373C  attggtttggctgatagtagttaacCGTTTGAAGGCGCGACACAA
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HPV15    62      YLR373C  gtttggctgatagtagttaacaacaCGTTTGAAGGCGCGACACAA
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HPV15    63      YLR373C  tttggctgatagtagttaacaacaaCGTTTGAAGGCGCGACACAA
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ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagagagctatatggataggccaaa      53      58      15
HPV15    330     YLR373C  aggaagattttgtttttgcctgttgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaaggtctgcagttaatttggact      52      52      15
HPV15    332     YLR373C  gaagattttgtttttgcctgttgttCGTTTGAAGGCGCGACACAA
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HPV15    424     YLR373C  ggaaatagagatagtagaacagaagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttttatgaacagtcggtgtgtagtt      52      52      21
HPV15    425     YLR373C  gaaatagagatagtagaacagaagcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttatgaacagtcggtgtgtagttg      53      52      21
HPV15    426     YLR373C  aaatagagatagtagaacagaagccCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttatgaacagtcggtgtgtagttgg      55      52      19
HPV15    434     YLR373C  atagtagaacagaagcctgttggagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtcggtgtgtagttgggaaataga      55      55      21
HPV15    438     YLR373C  tagaacagaagcctgttggagatatCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtgtgtagttgggaaatagagata      53      55      19
HPV15    449     YLR373C  cctgttggagatattattattcgctCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggaaatagagatagtagaacagaa      52      53      19
HPV15    586     YLR373C  ggcgatagaatgattgggaaagaagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggaaaggattgtgtagacattgta      52      55      19
HPV15    587     YLR373C  gcgatagaatgattgggaaagaagcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggaaaggattgtgtagacattgtag      53      55      19
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HPV15	588	YLR373C	cgatagaatgattgggaaagaagctCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaaggattgtgtagacattgtagg				53	55	19
HPV15	590	YLR373C	atagaatgattgggaaagaagctacCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaggattgtgtagacattgtagggc				55	52	19
HPV15	594	YLR373C	aatgattgggaaagaagctactataCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattgtgtagacattgtagggcgata				53	52	19
HPV15	608	YLR373C	aagctactataccagatatagtgctCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtagggcgatagaatgattgggaaa				55	53	17
HPV15	611	YLR373C	ctactataccagatatagtgcttgaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggcgatagaatgattgggaaagaa				55	53	19
HPV15	682	YLR373C	ttaagtgaagaagagacagaggaggCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcactgacctgcattgctacgaaga				58	55	21
HPV15	695	YLR373C	agacagaggaggagccacgatttatCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgctacgaagagttaagtgaagaa				52	58	17
HPV15	697	YLR373C	acagaggaggagccacgatttattcCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgctacgaagagttaagtgaagaaga				53	57	19
HPV15	701	YLR373C	aggaggagccacgatttattccttaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgaagagttaagtgaagaagagaca				53	57	19
HPV15	763	YLR373C	cttcgacttatagtggttgcaactcCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttccgtgttgcttttgtgattccaa				53	55	19
HPV15	768	YLR373C	acttatagtggttgcaactccatttCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgttgcttttgtgattccaagcttc				53	53	19
HPV15	778	YLR373C	gttgcaactccatttggaattcgctCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgattccaagcttcgacttatagt				53	57	19
HPV15	779	YLR373C	ttgcaactccatttggaattcgctcCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgattccaagcttcgacttatagtg				53	55	19
HPV15	782	YLR373C	caactccatttggaattcgctcacaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttccaagcttcgacttatagtggtt				53	57	17
HPV15	794	YLR373C	gaattcgctcacaacaagacttattCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacttatagtggttgcaactccattt				52	53	17
HPV15	795	YLR373C	aattcgctcacaacaagacttattaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttatagtggttgcaactccatttg				53	52	17
HPV15	801	YLR373C	ctcacaacaagacttattattggaaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtggttgcaactccatttggaattc				55	52	19
HPV15	855	YLR373C	agagaagcttcgccatgtctgatgaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttaagttggtgtgtccagggtgtc				58	58	19

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HPV15    857     YLR373C  agaagcttcgccatgtctgatgacaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaagttggtgtgtccagggtgtcga      58      58      19
HPV15    885     YLR373C  gtacatatgatcctaaagaaggctgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagcttcgccatgtctgatgacaaa      55      53      17
HPV15    894     YLR373C  atcctaaagaaggctgtagtgattgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatgtctgatgacaaaggtacatat      52      53      19
HPV15    948     YLR373C  ctagtttagatggtgatttggaaaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgttctagaagcagaatgctctgat      53      52      21
HPV15    1150    YLR373C  cctgcagtgtatatctatttcgccaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaagaggttttgcagcttagccctc      58      57      15
HPV15    1172    YLR373C  ccacagcataagtctaaaaggagatCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctcgcctgcagtgtatatctatttc      55      55      17
HPV15    1760    YLR373C  ataaatcaccaaacagcagaagctaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgagtggataatgacacaaacaat      52      53      21
HPV15    1866    YLR373C  caaaattagcagatacagatgcaaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaagcagaaattgcttggcattat      52      52      19
HPV15    1878    YLR373C  atacagatgcaaacgcgagagcattCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcttggcattatgcaaaattagca      52      57      17
HPV15    1895    YLR373C  agagcatttttacagcataacagtcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaattagcagatacagatgcaaacgc      53      52      21
HPV15    1897    YLR373C  agcatttttacagcataacagtcagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttagcagatacagatgcaaacgcga      55      52      21
HPV15    1910    YLR373C  cataacagtcaggcaagacttgtcaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgcaaacgcgagagcattttttaca      53      57      17
HPV15    3078    YLR373C  actatcatggcgcatattatttggaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatggaacaaggtggaaggaaaaatt      52      53      17
HPV15    3087    YLR373C  gcgcatattatttggaaggaactctCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtggaaggaaaaattgactatcat      52      55      15
HPV15    3088    YLR373C  cgcatattatttggaaggaactcttCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtggaaggaaaaattgactatcatg      52      53      15
HPV15    3172    YLR373C  ggaggtgcatgttaatgaggacactCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgccaggtttggcaaaactggaatct      57      58      15
HPV15    3173    YLR373C  gaggtgcatgttaatgaggacactaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccaggtttggcaaaactggaatctg      57      57      15
HPV15    3174    YLR373C  aggtgcatgttaatgaggacactatCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaggtttggcaaaactggaatctgg      57      55      15
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HPV15 3176 YLR373C gtgcatgttaatgaggacactatctCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtttggcaaaactggaatctggga	57	55	15		
HPV15 3177 YLR373C tgcatgttaatgaggacactatcttCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtttggcaaaactggaatctgggag	57	53	15		
HPV15 3417 YLR373C aagacacagcaaggcgatcaaggtcCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagaaaagacaaggacaaagacaa	53	58	19		
HPV15 3684 YLR373C gtagaaaacatactgggcgacttgaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgtgggaagctcagttcgatcactt	58	57	15		
HPV15 3685 YLR373C tagaaaacatactgggcgacttgaaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgggaagctcagttcgatcacttg	58	55	15		
HPV15 3700 YLR373C gcgacttgaaagattactggaagagCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgatcacttggtagaaaacatactg	53	55	15		
HPV15 3701 YLR373C cgacttgaaagattactggaagaggCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatcacttggtagaaaacatactgg	53	55	15		
HPV15 3703 YLR373C acttgaaagattactggaagaggctCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcacttggtagaaaacatactgggc	55	55	15		
HPV15 3839 YLR373C tcctgggtaggggtacaagtaatgCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagtaaaatactatagcaccacgtg	52	58	15		
HPV15 3844 YLR373C ggtaggggtacaagtaatgatagaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaatactatagcaccacgtggtcct	55	57	19		
HPV15 3845 YLR373C gtaggggtacaagtaatgatagaaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaatactatagcaccacgtggtcctg	57	55	17		
HPV15 3846 YLR373C taggggtacaagtaatgatagaatCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatactatagcaccacgtggtcctgg	58	53	17		
HPV15 3864 YLR373C atagaattggacgctcacgattgttCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtcctgggtagggggtacaagtaat	58	55	19		
HPV15 3868 YLR373C aattggacgctcacgattgttactgCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgggtagggggtacaagtaatgata	55	55	19		
HPV15 3873 YLR373C gacgctcacgattgttactggcattCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggggtacaagtaatgatagaatt	52	58	19		
HPV15 3874 YLR373C acgctcacgattgttactggcattcCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggggtacaagtaatgatagaattg	53	57	19		
HPV15 3877 YLR373C ctcacgattgttactggcattctctCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtacaagtaatgatagaattggac	52	57	21		
HPV15 3883 YLR373C attgttactggcattctcttccaacCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtaatgatagaattggacgctcac	53	53	17		

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HPV15   3887    YLR373C ttactggcattctcttccaacaccgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgatagaattggacgctcacgatt      53      57      17
HPV15   3893    YLR373C gcattctcttccaacaccgaaagagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaattggacgctcacgattgttact      55      57      15
HPV15   3952    YLR373C cgttgattggtcgctaggatatttaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcaaaataatgaaactgccaccag      52      55      17
HPV15   3954    YLR373C ttgattggtcgctaggatatttagaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaaaataatgaaactgccaccaggc      55      53      17
HPV15   3957    YLR373C attggtcgctaggatatttagatgaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaataatgaaactgccaccaggcgtt      55      53      19
HPV15   3961    YLR373C gtcgctaggatatttagatgatttaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgaaactgccaccaggcgttgatt      57      52      19
HPV15   4071    YLR373C tgcacgcagagtaaaacgtgcatctCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcactatactaacattcccatggccc      57      58      15
HPV15   4073    YLR373C cacgcagagtaaaacgtgcatctgtCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctatactaacattcccatggcccgt      57      58      15
HPV15   4097    YLR373C taactgacatttacaggggtgcaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcacgcagagtaaaacgtgcatct      57      57      15
HPV15   4103    YLR373C acatttacaggggtgcaaacaagcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagagtaaaacgtgcatctgtaact      53      57      17
HPV15   4352    YLR373C gtccagcggatgtaataccaattgaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccctggggtcacacctgaacttatt      58      57      15
HPV15   4358    YLR373C cggatgtaataccaattgatacagtCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtcacacctgaacttattggtcca      57      53      17
HPV15   4360    YLR373C gatgtaataccaattgatacagtcaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcacacctgaacttattggtccagc      57      52      15
HPV15   4376    YLR373C atacagtcacaccaattgaccccgcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtccagcggatgtaataccaatt      55      58      15
HPV15   4403    YLR373C cacctagtattgtcacaataactgaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacagtcacaccaattgaccccgca      58      53      15
HPV15   4431    YLR373C cagcgctgttgacctttacctgaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctagtattgtcacaataactgaca      52      58      15
HPV15   4434    YLR373C cgctgttgacctttacctgaattgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtattgtcacaataactgacagca      52      55      17
HPV15   4436    YLR373C ctgttgacctttacctgaattggaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtattgtcacaataactgacagcagc      53      55      17
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HPV15 4439 YLR373C ttgacctttacctgaattggagacCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtcacaataactgacagcagcgct	57	53	15		
HPV15 4442 YLR373C acctttacctgaattggagacaatCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacaataactgacagcagcgctgtt	57	53	15		
HPV15 4459 YLR373C gagacaattgcagaaatacatcctgCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcgctgttgacctttacctgaatt	55	53	13		
HPV15 4460 YLR373C agacaattgcagaaatacatcctgtCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgctgttgacctttacctgaattg	55	53	13		
HPV15 4469 YLR373C cagaaatacatcctgtaccaacagaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctttacctgaattggagacaatt	52	55	15		
HPV15 4562 YLR373C atcccagtcctcctgtacgaacaagCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttccagcgctattttagaagttgct	53	58	17		
HPV15 4577 YLR373C tacgaacaagagtgtctcgcacacaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaagttgctgatcccagtcctcct	58	58	19		
HPV15 4653 YLR373C cgaatctgcactagcagatcacgttCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattactgagtctacacctttgtctg	53	58	15		
HPV15 4655 YLR373C aatctgcactagcagatcacgttatCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtactgagtctacacctttgtctggc	57	55	15		
HPV15 4661 YLR373C cactagcagatcacgttattgttttCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtctacacctttgtctggcgaatct	57	53	17		
HPV15 4667 YLR373C cagatcacgttattgtttttgaaggCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacctttgtctggcgaatctgcacta	57	52	17		
HPV15 4676 YLR373C ttattgtttttgaaggtagtggaggCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggcgaatctgcactagcagatcac	58	52	15		
HPV15 4682 YLR373C tttttgaaggtagtggaggtcaaaaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatctgcactagcagatcacgttatt	53	53	15		
HPV15 4692 YLR373C tagtggaggtcaaaatataggcggtCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagatcacgttattgtttttgaag	52	57	15		
HPV15 4698 YLR373C aggtcaaaatataggcggttctcgcCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacgttattgtttttgaaggtagtg	52	57	15		
HPV15 4742 YLR373C cacaggaaagttttgaaatgcaaacCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttctcgcagtgctgctttggatgca	58	52	15		
HPV15 4785 YLR373C ttttgaaatacaagaaggtacaccaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgcaaacatggcctagtagataca	53	52	17		
HPV15 4815 YLR373C atctagcactcctgttcaaagagcaCGTTTGAAGGCGCGACACAA					
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaatacaagaaggtacaccaccaa	53	57	17		

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HPV15 4829 YLR373C ttcaaagagcagtacaatccctttcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacaccaccaagatctagcactcct 57 53 15
HPV15 4838 YLR373C cagtacaatccctttctagtcttagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagatctagcactcctgttcaaaga 53 53 15
HPV15 4841 YLR373C tacaatccctttctagtcttagaagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatctagcactcctgttcaaagagca 55 52 17
HPV15 4857 YLR373C tcttagaagggctttatataacagaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaaagagcagtacaatccctttcta 53 52 15
HPV15 4863 YLR373C aagggctttatataacagacggctgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagtacaatccctttctagtctta 53 55 15
HPV15 4866 YLR373C ggctttatataacagacggctgactCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtacaatccctttctagtcttagaa 52 57 17
HPV15 4867 YLR373C gctttatataacagacggctgactgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacaatccctttctagtcttagaag 52 55 17
HPV15 4868 YLR373C ctttatataacagacggctgactgaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaatccctttctagtcttagaagg 53 55 17
HPV15 4884 YLR373C gctgactgaacaagtagctgtaacaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttagaagggctttatataacagac 52 57 15
HPV15 4885 YLR373C ctgactgaacaagtagctgtaacagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttagaagggctttatataacagacg 52 55 15
HPV15 4888 YLR373C actgaacaagtagctgtaacagaccCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaagggctttatataacagacggct 55 55 17
HPV15 4892 YLR373C aacaagtagctgtaacagacccttTCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggctttatataacagacggctgact 55 55 17
HPV15 4898 YLR373C tagctgtaacagacccttattcttCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatataacagacggctgactgaacaa 53 53 17
HPV15 4901 YLR373C ctgtaacagacccttattcttgggCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaacagacggctgactgaacaagta 55 55 17
HPV15 4904 YLR373C taacagacccttattcttgggacgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagacggctgactgaacaagtagct 58 55 17
HPV15 4910 YLR373C acccttattcttgggacgaccctcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgctgactgaacaagtagctgtaaca 55 58 17
HPV15 4929 YLR373C accctcacgcttggtgcaatttcaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtaacagacccttattcttgggac 55 58 15
HPV15 4938 YLR373C cttggtgcaatttcaatttgacaatCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctttattcttgggacgaccctcac 58 52 15

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HPV15    4942    YLR373C gtgcaatttcaatttgacaatccaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtattcttgggacgaccctcacgctt      58      52      17
HPV15    5030    YLR373C ataggcaatttctagatgtagttcgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgttgaagcatttgaagagcctcca      55      52      17
HPV15    5034    YLR373C gcaatttctagatgtagttcgcctaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaagcatttgaagagcctccagata      55      55      15
HPV15    5035    YLR373C caatttctagatgtagttcgcctagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagcatttgaagagcctccagatag      55      53      15
HPV15    5048    YLR373C tagttcgcctaggaaggcctacttaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcctccagataggcaatttctagat      55      58      15
HPV15    5051    YLR373C ttcgcctaggaaggcctacttattcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccagataggcaatttctagatgta      52      57      15
HPV15    5055    YLR373C cctaggaaggcctacttattctgaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgataggcaatttctagatgtagttc      52      57      15
HPV15    5064    YLR373C gcctacttattctgaaacaccacaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttctagatgtagttcgcctaggaa      53      55      15
HPV15    5065    YLR373C cctacttattctgaaacaccacaagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttctagatgtagttcgcctaggaag      55      53      15
HPV15    5078    YLR373C aaacaccacaaggttatgtgcgtgtCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcgcctaggaaggcctacttattct      57      57      17
HPV15    5098    YLR373C cgtgtaagtagacttggtagacgggCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattctgaaacaccacaaggttatgt      52      58      19
HPV15    5100    YLR373C tgtaagtagacttggtagacgggccCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctgaaacaccacaaggttatgtgc      55      58      19
HPV15    5106    YLR373C tagacttggtagacgggccacaattCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaccacaaggttatgtgcgtgtaa      55      58      15
HPV15    5109    YLR373C acttggtagacgggccacaattagaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccacaaggttatgtgcgtgtaagta      55      58      17
HPV15    5114    YLR373C gtagacgggccacaattagaaccagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggttatgtgcgtgtaagtagactt      53      58      17
HPV15    5133    YLR373C aaccagaagtggtgcacaagttggtCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagacttggtagacgggccacaatta      57      58      17
HPV15    5139    YLR373C aagtggtgcacaagttggtgctcaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtagacgggccacaattagaacca      58      58      17
HPV15    5244    YLR373C taccattgttcaggctcctatggaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttactaggagaacattcaggtgata      52      57      17
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HPV15 5257 YLR373C gctcctatggaaagttcatttatagCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattcaggtgatagtaccattgttca 52 52 15
HPV15 5258 YLR373C ctcctatggaaagttcatttatagaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttcaggtgatagtaccattgttcag 53 52 15
HPV15 5327 YLR373C acagtactgaagcagatgacattgaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgattcattacatgtgggcctacag 55 55 19
HPV15 5339 YLR373C cagatgacattgattacaattctgcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgggcctacaggacagtactgaa 58 52 17
HPV15 5430 YLR373C gcgcagcactacaacatatacagtaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtctcatttggtgtttggcaatacac 53 57 15
HPV15 5431 YLR373C cgcagcactacaacatatacagtacCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctcatttggtgtttggcaatacacg 55 55 15
HPV15 5433 YLR373C cagcactacaacatatacagtacctCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatttggtgtttggcaatacacggc 57 55 15
HPV15 5436 YLR373C cactacaacatatacagtacctagaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttggtgtttggcaatacacggcgca 58 53 17
HPV15 5453 YLR373C tacctagatttgaatcacctagaaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacggcgcagcactacaacatataca 57 52 15
HPV15 5460 YLR373C atttgaatcacctagaaatactgggCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagcactacaacatatacagtaccta 52 52 15
HPV15 5485 YLR373C ttttacatacaagatgtgcatgggtCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatttgaatcacctagaaatactgg 52 53 17
HPV15 5507 YLR373C ggtataatgtagcctatccggagtcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgggttttacatacaagatgtgcat 52 57 21
HPV15 5508 YLR373C gtataatgtagcctatccggagtccCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgggttttacatacaagatgtgcatg 53 57 21
HPV15 5509 YLR373C tataatgtagcctatccggagtcccCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggttttacatacaagatgtgcatgg 53 57 21
HPV15 5527 YLR373C gagtcccgtgatactaccgaaataaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcatgggtataatgtagcctatcc 55 57 17
HPV15 5528 YLR373C agtcccgtgatactaccgaaataatCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcatgggtataatgtagcctatccg 57 55 17
HPV15 5530 YLR373C tcccgtgatactaccgaaataatatCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgggtataatgtagcctatccgga 55 53 17
HPV15 5582 YLR373C ttataaattttgaagaggcaggtggCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccacaatctgacacgccaactgta 57 52 15

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HPV15	5628	YLR373C	cttaaaaacacgtaaacgaaaacgcCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtggagactattatttacatccaa				52	52	17
HPV15	5694	YLR373C	acgacgggtaaagtatatttgccacCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttttacagatgacattgtggctacc				53	55	17
HPV15	5697	YLR373C	acgggtaaagtatatttgccaccaaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacagatgacattgtggctaccgac				57	55	19
HPV15	5700	YLR373C	ggtaaagtatatttgccaccaacacCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagatgacattgtggctaccgacgac				58	53	19
HPV15	5707	YLR373C	tatatttgccaccaacaccacctgtCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattgtggctaccgacgacgggtaaa				58	57	17
HPV15	5731	YLR373C	tagcacgtgtacaaagcaccgatgaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtatatttgccaccaacaccacct				55	58	15
HPV15	5734	YLR373C	cacgtgtacaaagcaccgatgaataCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatatttgccaccaacaccacctgta				55	57	15
HPV15	5747	YLR373C	caccgatgaatatgtggagagaactCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacaccacctgtagcacgtgtacaaa				57	57	17
HPV15	5752	YLR373C	atgaatatgtggagagaactaatgtCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacctgtagcacgtgtacaaagcacc				58	52	15
HPV15	5812	YLR373C	tagggcatccctactttgatgttagCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcaatgagtgaccgtctgttaaca				55	55	17
HPV15	5816	YLR373C	gcatccctactttgatgttagatctCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgagtgaccgtctgttaacagtag				55	55	17
HPV15	5817	YLR373C	catccctactttgatgttagatctgCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgagtgaccgtctgttaacagtagg				57	53	17
HPV15	5830	YLR373C	atgttagatctgttaatggaggtagCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttaacagtagggcatccctacttt				55	52	17
HPV15	5833	YLR373C	ttagatctgttaatggaggtagcatCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacagtagggcatccctactttgat				55	53	19
HPV15	5837	YLR373C	atctgttaatggaggtagcatagaaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtagggcatccctactttgatgtta				55	53	17
HPV15	5842	YLR373C	ttaatggaggtagcatagaagttccCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcatccctactttgatgttagatct				53	53	19
HPV15	5855	YLR373C	catagaagttcctaaagtgtctggaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgttagatctgttaatggaggta				52	55	17
HPV15	5860	YLR373C	aagttcctaaagtgtctggaaatcaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagatctgttaatggaggtagcata				52	53	15

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HPV15	5878	YLR373C	gaaatcaatatagagcatttagggtCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagcatagaagttcctaaagtgtct				52	52	19
HPV15	6100	YLR373C	atgacaggcaaaatacatcttttgaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagtaattatcaaggcaactctact				52	52	19
HPV15	6132	YLR373C	caggttcaaatgtttgtagtaggctCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcaaaatacatcttttgacccaaa				52	55	17
HPV15	6136	YLR373C	ttcaaatgtttgtagtaggctgtgtCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaatacatcttttgacccaaagcag				52	53	17
HPV15	6200	YLR373C	tgaatcagagagaaataatcaggcgCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaacactgggatagagctcttgttt				55	53	17
HPV15	6202	YLR373C	aatcagagagaaataatcaggcgggCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacactgggatagagctcttgtttgt				55	55	17
HPV15	6210	YLR373C	agaaataatcaggcgggaaaatgtcCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatagagctcttgtttgtgaatcaga				52	53	15
HPV15	6225	YLR373C	ggaaaatgtcctcctttggaacttaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgaatcagagagaaataatcaggc				53	55	15
HPV15	6226	YLR373C	gaaaatgtcctcctttggaacttaaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgaatcagagagaaataatcaggcg				53	53	15
HPV15	6334	YLR373C	atgtgagtctggatatagtgaatgaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaaggccttatcagttactaagtca				53	53	17
HPV15	6337	YLR373C	tgagtctggatatagtgaatgaaacCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggccttatcagttactaagtcagat				53	52	17
HPV15	6339	YLR373C	agtctggatatagtgaatgaaacttCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccttatcagttactaagtcagatgt				52	52	15
HPV15	6352	YLR373C	tgaatgaaacttgcaaatatccagaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaagtcagatgtgagtctggatata				52	52	17
HPV15	6412	YLR373C	cttgtttttttttttgcaagacgagaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtatggcaaatgatgtgtatggagac				53	52	17
HPV15	6434	YLR373C	agaacagtgctatgctagacattacCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacgcttgtttttttttttgcaagac				52	53	17
HPV15	6436	YLR373C	aacagtgctatgctagacattacttCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgcttgtttttttttttgcaagacga				52	53	17
HPV15	6482	YLR373C	tgatgctcttcctgatgcagctgtcCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtactttgtcagaggaggtgcagtag				57	58	19
HPV15	6496	YLR373C	atgcagctgtcaatcaagatcataaCGTTTGAAGGCGCGACACAA			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggtgcagtaggtgatgctcttcct				58	53	17

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HPV15 6499 YLR373C cagctgtcaatcaagatcataatttCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcagtaggtgatgctcttcctgat 57 52 17
HPV15 6604 YLR373C tgacatctgatgctcagctgtttaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctttcccacagttagtggttcttta 53 55 17
HPV15 6613 YLR373C atgctcagctgtttaatagaccgttCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagttagtggttctttagtgacatct 52 55 15
HPV15 6621 YLR373C ctgtttaatagaccgttttggttaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttctttagtgacatctgatgctca 53 52 15
HPV15 6632 YLR373C accgttttggttaagaagagctcaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacatctgatgctcagctgtttaata 52 55 15
HPV15 6636 YLR373C ttttggttaagaagagctcaagggcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgatgctcagctgtttaatagacc 55 55 15
HPV15 6658 YLR373C ggcataacaatggcatactttggggCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccgttttggttaagaagagctcaa 53 57 17
HPV15 6670 YLR373C gcatactttggggtaatcagatgttCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagaagagctcaagggcataacaat 53 55 15
HPV15 6671 YLR373C catactttggggtaatcagatgtttCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagaagagctcaagggcataacaatg 55 53 15
HPV15 6680 YLR373C gggtaatcagatgtttattactgttCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaagggcataacaatggcatacttt 53 52 15
HPV15 6922 YLR373C ggtttgttcctacaccagacaacgcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggtattttagaagactggcaacta 52 58 15
HPV15 6923 YLR373C gtttgttcctacaccagacaacgctCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtattttagaagactggcaactag 53 58 15
HPV15 6924 YLR373C tttgttcctacaccagacaacgctgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtattttagaagactggcaactagg 53 57 15
HPV15 6928 YLR373C ttcctacaccagacaacgctgtacaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtttagaagactggcaactagggttt 53 58 15
HPV15 6997 YLR373C atgctgtacaaccaaaggacaaagaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgactctaaggcaactaaatgtcct 53 55 17
HPV15 7021 YLR373C aagacccatttggaaagtatacattCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatgctgtacaaccaaaggacaaa 53 52 17
HPV15 7193 YLR373C tacatgaccgatttcggtcgctaatCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtttctaaaggtactaaacgcaaac 52 57 17
HPV15 7199 YLR373C accgatttcggtcgctaataaacaaCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaaggtactaaacgcaaacgtacat 52 55 21

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HPV15   7298    YLR373C cacccggttaatcagatataaaatgCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccgcataggtcattgccaacaacc      58      52      13
HPV15   7334    YLR373C attttatcaccgcttttgtggaagcCGTTTGAAGGCGCGACACAA
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatcagatataaaatgcacctggtgc      53      53      17
HPV16   191     YER162C cgacgtgaggtatatgactttgcttGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtgtactgcaagcaacagttact      55      57      17
HPV16   193     YER162C acgtgaggtatatgactttgcttttGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtactgcaagcaacagttactgc      57      53      17
HPV16   196     YER162C tgaggtatatgactttgcttttcggGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtactgcaagcaacagttactgcgac      57      53      13
HPV16   198     YER162C aggtatatgactttgcttttcgggaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgcaagcaacagttactgcgacgt      58      55      15
HPV16   200     YER162C gtatatgactttgcttttcgggattGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcaagcaacagttactgcgacgtga      58      53      15
HPV16   201     YER162C tatatgactttgcttttcgggatttGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaagcaacagttactgcgacgtgag      58      52      17
HPV16   207     YER162C actttgcttttcgggatttatgcatGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacagttactgcgacgtgaggtatat      55      53      17
HPV16   234     YER162C tatatagagatgggaatccatatgcGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctttgcttttcgggatttatgcata      52      52      21
HPV16   470     YER162C tggaccggtcgatgtatgtcttgttGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaagattccataatataaggggtcg      52      58      19
HPV16   472     YER162C gaccggtcgatgtatgtcttgttgcGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagattccataatataaggggtcggt      53      58      19
HPV16   473     YER162C accggtcgatgtatgtcttgttgcaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgattccataatataaggggtcggtg      55      58      19
HPV16   478     YER162C tcgatgtatgtcttgttgcagatcaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcataatataaggggtcggtggaccg      58      55      21
HPV16   530     YER162C taatcatgcatggagatacacctacGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaagaacacgtagagaaacccagct      57      53      19
HPV16   640     YER162C gatgaaatagatggtccagctggacGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaattaaatgacagctcagaggagga      53      57      21
HPV16   727     YER162C cttcggttgtgcgtacaaagcacacGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccttttgttgcaagtgtgactctac      55      58      17
HPV16   732     YER162C gttgtgcgtacaaagcacacacgtaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgttgcaagtgtgactctacgcttc      57      58      17
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HPV16	733	YER162C	ttgtgcgtacaaagcacacacgtagGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttgcaagtgtgactctacgcttcg				58	57	19	
HPV16	736	YER162C	tgcgtacaaagcacacacgtagacaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcaagtgtgactctacgcttcggtt				58	58	19	
HPV16	738	YER162C	cgtacaaagcacacacgtagacattGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagtgtgactctacgcttcggttgt				57	57	21	
HPV16	1055	YER162C	cacaggaagcaaaacaacatagagaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagagacagcacatgcgttgtttact				55	55	15	
HPV16	1124	YER162C	tgatattagtggatgtgtagacaatGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacgaaagtatttggtagtccactta				52	52	17	
HPV16	1249	YER162C	aagtggaaactcagcagatgttacaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgaagacagcgggtatggcaatact				58	55	21	
HPV16	1255	YER162C	aaactcagcagatgttacaggtagaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagcgggtatggcaatactgaagtg				58	55	21	
HPV16	1284	YER162C	cgccatgagactgaaacaccatgtaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctcagcagatgttacaggtagaagg				57	58	17	
HPV16	1291	YER162C	agactgaaacaccatgtagtcagtaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgatgttacaggtagaagggcgccat				58	55	15	
HPV16	1364	YER162C	gggagagggtgttagtgaaagacacGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcagtcagtacagtagtggaagtg				57	58	15	
HPV16	1365	YER162C	ggagagggtgttagtgaaagacacaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcagtcagtacagtagtggaagtgg				58	58	15	
HPV16	1371	YER162C	ggtgttagtgaaagacacactatatGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtacagtagtggaagtgggggaga				58	53	15	
HPV16	3021	YER162C	ccttgaagtgtatttaactgcaccaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgaaaagtggacattacaagacgtta				52	55	17	
HPV16	3026	YER162C	aagtgtatttaactgcaccaacaggGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtggacattacaagacgttagcctt				55	53	17	
HPV16	3029	YER162C	tgtatttaactgcaccaacaggatgGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgacattacaagacgttagccttgaa				53	53	17	
HPV16	3031	YER162C	tatttaactgcaccaacaggatgtaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcattacaagacgttagccttgaagt				53	53	17	
HPV16	3041	YER162C	caccaacaggatgtataaaaaaacaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcgttagccttgaagtgtatttaact				52	52	17	
HPV16	3088	YER162C	tttgatggagacatatgcaatacaaGGCATCAATCTGTTGCACGG				
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacatggatatacagtggaagtgca				53	52	17	

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HPV16	3092	YER162C	atggagacatatgcaatacaatgcaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggatatacagtggaagtgcagttt				53	53	17
HPV16	3095	YER162C	gagacatatgcaatacaatgcattaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatatacagtggaagtgcagtttgat				52	52	17
HPV16	3175	YER162C	ggtcaagttgactattatggtttatGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaagaagcatcagtaactgtggtaga				53	52	19
HPV16	3293	YER162C	gtggtcaggtaatattatgtcctacGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaataaagtatgggaagttcatgcg				52	53	19
HPV16	3294	YER162C	tggtcaggtaatattatgtcctacaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaataaagtatgggaagttcatgcgg				53	53	17
HPV16	3296	YER162C	gtcaggtaatattatgtcctacatcGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaagtatgggaagttcatgcgggt				55	52	19
HPV16	3297	YER162C	tcaggtaatattatgtcctacatctGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaagtatgggaagttcatgcgggtg				57	52	19
HPV16	3312	YER162C	tcctacatctgtgtttagcagcaacGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatgcgggtggtcaggtaatattat				55	55	19
HPV16	3333	YER162C	caacgaagtatcctctcctgaaattGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttatgtcctacatctgtgtttagca				52	55	17
HPV16	3341	YER162C	tatcctctcctgaaattattaggcaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtacatctgtgtttagcagcaacgaa				53	53	15
HPV16	3353	YER162C	aaattattaggcagcacttggccaaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtagcagcaacgaagtatcctctcct				57	55	17
HPV16	3504	YER162C	agactcagtggacagtgctccaatcGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgccacaccactaagttgttgcaca				57	58	17
HPV16	3519	YER162C	tgctccaatcctcactgcatttaacGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgttgcacagagactcagtggaca				57	55	17
HPV16	3521	YER162C	ctccaatcctcactgcatttaacagGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgttgcacagagactcagtggacagt				58	55	17
HPV16	3536	YER162C	catttaacagctcacacaaaggacgGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagtggacagtgctccaatcctcact				58	55	17
HPV16	3546	YER162C	ctcacacaaaggacggattaactgtGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgctccaatcctcactgcatttaaca				55	57	21
HPV16	3557	YER162C	gacggattaactgtaatagtaacacGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcactgcatttaacagctcacacaaa				53	52	17
HPV16	3558	YER162C	acggattaactgtaatagtaacactGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactgcatttaacagctcacacaaag				53	52	17

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HPV16	3570	YER162C	taatagtaacactacacccatagtaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagctcacacaaaggacggattaact				55	52 17
HPV16	3576	YER162C	taacactacacccatagtacatttaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacaaaggacggattaactgtaata				52	52 17
HPV16	3673	YER162C	tcgtctacatggcattggacaggacGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagcattgtacattgtatactgcagt				52	58 15
HPV16	3676	YER162C	tctacatggcattggacaggacataGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattgtacattgtatactgcagtgtc				52	57 15
HPV16	3858	YER162C	gcgtgctttttgctttgcttttgtgGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttgatactgcatccacaacattact				52	55 17
HPV16	3859	YER162C	cgtgctttttgctttgcttttgtgtGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgatactgcatccacaacattactg				53	55 17
HPV16	3861	YER162C	tgctttttgctttgcttttgtgtgcGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatactgcatccacaacattactggc				55	53 15
HPV16	3863	YER162C	cttttgctttgcttttgtgtgcttGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactgcatccacaacattactggcgt				57	53 17
HPV16	3870	YER162C	ctttgcttttgtgtgcttttgtgtgGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccacaacattactggcgtgcttttt				55	53 17
HPV16	3875	YER162C	cttttgtgtgcttttgtgtgtctgcGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacattactggcgtgcttttgcttt				53	55 17
HPV16	3883	YER162C	tgcttttgtgtgtctgcctattaatGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggcgtgcttttgctttgcttttgt				55	53 17
HPV16	3895	YER162C	tctgcctattaatacgtccgctgctGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgctttgcttttgtgtgcttttgtgt				53	58 17
HPV16	3899	YER162C	cctattaatacgtccgctgcttttgGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcttttgtgtgcttttgtgtgtct				53	55 17
HPV16	3911	YER162C	tccgctgcttttgtctgtgtctacaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttttgtgtgtctgcctattaatac				52	58 17
HPV16	3915	YER162C	ctgcttttgtctgtgtctacatacaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgtgtgtctgcctattaatacgtcc				55	55 15
HPV16	3918	YER162C	cttttgtctgtgtctacatacacatGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgtctgcctattaatacgtccgct				57	53 15
HPV16	3924	YER162C	tctgtgtctacatacacatcattaaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgcctattaatacgtccgctgctttt				55	52 15
HPV16	3982	YER162C	cctctgcgtttaggtgttttattgtGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtattactattgtggataacagca				52	55 15

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HPV16    4228    YER162C caaaacgcacaaaacgtgcatcggcGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcttaacaatgcgacacaaacgttct      53      58      17
HPV16    4251    YER162C gctacccaactttataaaacatgcaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctgcaaaacgcacaaaacgtgcatc      57      53      15
HPV16    4252    YER162C ctacccaactttataaaacatgcaaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcaaaacgcacaaaacgtgcatcg      57      52      15
HPV16    4314    YER162C gttgaaggcaaaactattgctgaacGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcatgtccacctgacattatacctaa      53      53      15
HPV16    4315    YER162C ttgaaggcaaaactattgctgaacaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgtccacctgacattatacctaag      53      53      15
HPV16    4318    YER162C aaggcaaaactattgctgaacaaatGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccacctgacattatacctaaggtt      53      52      15
HPV16    4474    YER162C taagacccccttaacagtagatccGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacagctacagatacacttgctcct      57      55      15
HPV16    4478    YER162C acccccttaacagtagatcctgtgGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgctacagatacacttgctcctgtaa      55      57      15
HPV16    4504    YER162C gcccttctgatccttctatagtttcGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacccccttaacagtagatcctgtg      57      55      21
HPV16    4505    YER162C cccttctgatccttctatagtttctGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccccctttaacagtagatcctgtgg      58      55      21
HPV16    4513    YER162C atccttctatagtttctttagtggaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaacagtagatcctgtgggcccttct      58      52      21
HPV16    4576    YER162C taccttccattcccccagatgtatcGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtattgatgctggtgcaccaacatct      55      57      17
HPV16    4610    YER162C tattactacttcaactgataccacaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattcccccagatgtatcaggattta      53      52      17
HPV16    4732    YER162C cagaaactggagggcattttacactGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatctgtattgcagcctccaacacct      57      57      15
HPV16    5061    YER162C gatatagttgctttacataggccagGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatatagctccagatcctgacttttt      52      53      17
HPV16    5068    YER162C ttgctttacataggccagcattaacGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtccagatcctgacttttttggatata      52      53      17
HPV16    5153    YER162C tagtggaaaatctataggtgctaagGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggtaataaacaaacactacgtactc      52      52      19
HPV16    5158    YER162C gaaaatctataggtgctaaggtacaGGCATCAATCTGTTGCACGG
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaacaaacactacgtactcgtagt      52      53      19
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HPV16	5159	YER162C	aaaatctataggtgctaaggtacatGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaacaaacactacgtactcgtagtg				53	52	21
HPV16	5507	YER162C	gtctccacaatatacaattattgctGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccttcattaattcctatagttccag				52	52	15
HPV16	5650	YER162C	cctcctgtcccagtatctaaggttgGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcctagtgaggccactgtctactt				58	58	17
HPV16	5679	YER162C	cacggatgaatatgttgcacgcacaGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcctgtcccagtatctaaggttgtaa				55	58	19
HPV16	5693	YER162C	ttgcacgcacaaacatatattatcaGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaaggttgtaagcacggatgaatat				52	52	15
HPV16	6011	YER162C	cttatgcagcaaatgcaggtgtggaGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCattggatgacacagaaaatgctagt				52	58	15
HPV16	6017	YER162C	cagcaaatgcaggtgtggataatagGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgacacagaaaatgctagtgcttat				52	55	17
HPV16	6026	YER162C	caggtgtggataatagagaatgtatGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaaatgctagtgcttatgcagcaaat				52	53	19
HPV16	6158	YER162C	gtgattgtccaccattagagttaatGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCatgtaccaatgttgcagtaaatcca				52	53	17
HPV16	6165	YER162C	tccaccattagagttaataaacacaGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaatgttgcagtaaatccaggtgatt				52	52	17
HPV16	6211	YER162C	gttcatactggctttggtgctatggGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacacagttattcaggatggtgatat				52	57	17
HPV16	6212	YER162C	ttcatactggctttggtgctatggaGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcacagttattcaggatggtgatatg				53	57	17
HPV16	6221	YER162C	gctttggtgctatggactttactacGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtcaggatggtgatatggttcatact				53	55	17
HPV16	6222	YER162C	ctttggtgctatggactttactacaGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaggatggtgatatggttcatactg				55	55	17
HPV16	6235	YER162C	gactttactacattacaggctaacaGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggttcatactggctttggtgctat				55	53	17
HPV16	6236	YER162C	actttactacattacaggctaacaaGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggttcatactggctttggtgctatg				57	52	17
HPV16	6253	YER162C	gctaacaaaagtgaagttccactggGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCgtgctatggactttactacattaca				52	55	17
HPV16	6428	YER162C	acgatttatacattaaaggctctggGGCATCAATCTGTTGCACGG			
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtggtactgttggtgaaaatgtacca				53	52	15

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HPV16	6431	YER162C	atttatacattaaaggctctgggtcGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtactgttggtgaaaatgtaccagac				53	52	17
HPV16	6454	YER162C	tctactgcaaatttagccagttcaaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCacgatttatacattaaaggctctgg				52	53	19
HPV16	6470	YER162C	ccagttcaaattattttcctacaccGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaggctctgggtctactgcaaattta				55	52	17
HPV16	6563	YER162C	gccacaataatggcatttgttggggGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaccttattggttacaacgagcacag				55	57	15
HPV16	6564	YER162C	ccacaataatggcatttgttggggtGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCccttattggttacaacgagcacagg				57	57	15
HPV16	6585	YER162C	gggtaaccaactatttgttactgttGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcagggccacaataatggcatttgtt				55	53	17
HPV16	6710	YER162C	gggaggaatatgatttacagtttatGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtaactttaaggagtacctacgacat				52	52	19
HPV16	6817	YER162C	aattttggtctacaacctcccccagGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgaattccactattttggaggactg				53	57	15
HPV16	6881	YER162C	caattgcttgtcaaaaacatacaccGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCagatacttataggtttgtaacccag				52	52	17
HPV16	6911	YER162C	cacctaaagaagatgatcccctt aaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgcttgtcaaaaacatacacctcca				53	55	17
HPV16	7029	YER162C	attgaaggccaaaccaaaatttacaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCggacgcaaatttttactacaagcag				53	52	15
HPV16	7103	YER162C	ctaaacgcaaaaaacgtaagctgtaGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCcaccacctcatctacctctacaact				57	53	15
HPV16	7552	YER162C	cactgcttgccaaccattccattgtGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgccaaatccctgttttcctgacct				57	58	17
HPV16	7557	YER162C	cttgccaaccattccattgtttttt GGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCaatccctgttttcctgacctgcact				57	53	17
HPV16	7667	YER162C	ctgttaggcacatatttttggcttgGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCactatgcgccaacgccttacatacc				58	53	15
HPV16	7761	YER162C	ttcatacatgaactgtgtaaaggttGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCctaaggccaactaaatgtcacccta				55	52	15
HPV16	7822	YER162C	tgtgtgcaaaccgattttgggttacGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCtgttcatttgtaaaactgcacatgg				52	55	15
HPV16	7824	YER162C	tgtgcaaaccgattttgggttacacGGCATCAATCTGTTGCACGG		
ACGACGGGTTCTCATCTTGTUUUGCATGATCGACATCGGTCTCttcatttgtaaaactgcacatgggt				52	55	17

Petitioner Illumina, Inc., EX1003, p. 1109

Petitioner Illumina, Inc., EX1003, p. 1110

sometags.txt supplemental file : tagIDs and tag sequences

HPV16 — YER162C:GGCATCAATCTGTTGCACGG
YNL286W:AGGTCCGTATAGGTCTCGTC
HPV10 — YML001W:GTACGTGGAGATCGACATAA
HPV15 — YLR373C:CGTTTGAAGGCGCGACACAA
YER111C:CACAGGTTAATACGTGACAC
YNL216W:TAAACGGCTCGCTACGGGTA
YPR042C:ATCGACGACCTTACGAACAG
YJL130C:AGGTACAGAACCCACTACGG
YLR050C:CACGCCATACCAAGGAGAGT
YER183C:TTCAGTGACCTTACGGCTAG
HPV13 — YHL031C:ATCACCGAACCGCAGTTAAG
YOR322C:TCGACGTGACCTAAGTATCA
YMR025W:TAACTCGTGGGTAACTGCCG
YER013W:CACACGAGAAGAGCGACGTT
YLR212C:CATTGACCAAGGCCGACAGA
YBR200W:TTACACGGAAGTCGGAGCCA
YGL247W:AGGCATAGCCCTGACAGCAA
YBR209W:TACAGGGCTGCGGATCTACA
YNL189W:ATTGACGGAACTAGACAGCC
HPV12 — YDR286C:TCTTCCTCAGCCGTGGAGTT
YLR430W:TATAAAGGGTCTCACGCCGC
YKR054C:TATACGACTTGTGGCTCCGG
YPL030W:GGGAGTCCACCACGTTACTT
YBR110W:TCGAGGTAGCAGTGTTCCCA
YLR379W:TGTACTTCGCCGAGCTTACG
YBR239C:TGTGGACTCATCCGCGCTAA
YHL040C:AACGTCCTAAACGCAAGCGG
HPV11 — YBL072C:TTCGCCTGACTTGAAAGACG
YLR069C:ACACCGTCAAAGAGCCAGGT
YOL141W:TGCTACGTCCCTACGGTATA
YGL208W:ATAATCCGACCTGCTGGGCA
YDR210W:CTGATACCGCACAGTGGCAA
YNL182C:TGTCTCGATGCAGGTCTAGT
YER120W:TGTAGTACCCTTAGGCTCCG
HPV14d — YIL167W:GTCGCCAACGAGTGACAACA
YBL038W:TTCATCTGACTTGAGGCGCG
YOR050C:TGCTCGTCACTTAGGGCTAC
YGR069W:ACATACAACACCGCTTAGGG
YBL053W:TATGAACGCCTTCGATGCCG
YEL003W:ACCGTAGCAAAGTGGACGAC

Petitioner Illumina, Inc., EX1003, p. 1111

Electronic Patent Application Fee Transmittal	
Application Number:	15231687
Filing Date:	08-Aug-2016
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Sandra Richards
Attorney Docket Number:	MLB-002/04US 34468/10
Filed as Small Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	2251	1	100	100
Miscellaneous:				
		Total in USD ($)		**100**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 11/01/2019

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/01/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Applicant-Initiated Interview Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA (FITF) Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) STEVEN C. POHNERT PhD.

(2) Anne Kock.

(3) Thomas Meyers.

(4) Greg Porecca.

Date of Interview: 22 October 2019.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☑102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 68.

Identification of prior art discussed: Pourmand and Ronaghi.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The interview began with the representative providing his interpretation of the claims and the patentability. The discussion continued with inventor Porecca explaining how the claims as amended are different than the art of record. The examiner noted the arguments, but indicated further review of the art would be needed. The examiner noted a quick review of the specification did not reveal support for random locus independent differentiator tags. No agreement on patentability was reached..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☑ Attachment

/Steven Pohnert/
Primary Examiner, Art Unit 1634

Petitioner Illumina, Inc., EX1003, p. 1115

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.

TITLE: **METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**

AGENDA FOR WEBEX INTERVIEW ON OCTOBER 22, 2019 3:00 PM

Participants: Examiner Steven Pohnert, Inventor Greg Porreca, and Applicant's Representatives Thomas Meyers and Annie Kock

Agenda:

1. Introductions
2. Discuss the differences between the invention and references Pourmand (BMC Informatics, 2006, 7:500, p 1-10) and Ronaghi (US 2006/0008824) cited in the §§102 and 103 rejections.
3. Discuss the following proposed amendment to independent claim 68

68. (Currently Amended) A method for nucleic acid identification, the method comprising the steps of:

obtaining a biological sample comprising a plurality of target nucleic acid molecules;

tagging each ~~independently isolated~~ target nucleic acid molecule ~~of a plurality of target nucleic acid molecules obtained~~ from [[a]]the biological sample with a random ~~unique~~ locus-independent differentiator tag, thereby generating ~~to generate~~ a plurality of tagged target nucleic acid molecules, the differentiator tags remaining attached to the target nucleic acid molecules through amplification and sequencing steps to allow unique identification of each target nucleic acid molecule;

amplifying said uniquely tagged target nucleic acid molecules to generate amplicons that contain the uniquely tagged target nucleic acid molecules;

sequencing the amplicons obtained in said amplifying step, wherein each ~~unique~~ differentiator tag is sequenced along with the target nucleic acid molecule to allow each sequencing read to be linked to the target molecule from which it was derived; and

uniquely identifying ~~a sequence for~~ the target nucleic acid molecule based on identity of the differentiator tag ~~said nucleic acid molecules~~.

Contact Info: Annie Kock, (617) 856-8571, akock@brownrudnick.com

63526133 v1

Pohnert, Steven

From: Kock, Annie J. <AKock@brownrudnick.com>
Sent: Monday, October 21, 2019 11:27 AM
To: Pohnert, Steven
Subject: Interview Agenda; US Appl. No. 15/231,687; Attorney Docket No. MLB-002/04US 34468/10
Attachments: MLB-002-04US-InterviewAgenda.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Examiner Pohnert,

I am a registered patent attorney of record in the above-identified US patent application, and I authorize you to communicate with me by email about this application. I understand that email communications are not secure, but still authorize you to communicate with me by email about this application.

Please find the agenda attached for the video conference interview scheduled for **October 22, 2019 at 3:00 p.m.** Please send the WebEx link to this email address and to tmevers@brownrudnick.com and greg@molecularloop.com.

Kindly acknowledge receipt of this message by return email.

With kind regards,
Annie

brownrudnick

Annie J. Kock
Associate

Brown Rudnick LLP
One Financial Center
Boston, MA 02111
T: 617.856.8571
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****

Petitioner Illumina, Inc., EX1003, p. 1119

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 12/20/2019

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/20/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Office Action Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10/24/2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 68-78 and 80-83 is/are pending in the application.

5a) Of the above claim(s) 71-73 and 76-78 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68-70,74-75 and 80-83 is/are rejected.

8) ☑ Claim(s) 68-70,74-75 and 80-83 is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 10/21/2016 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Petitioner Illumina, Inc., EX1003, p. 1121

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Claim Status and Formal matters

This action is in response to papers filed 10/24/2019.

Claims 68-69 have been amended.

Claim 83 has been added by amendment.

Applicant's election without traverse of group I, claims 68-70, 74-75, 80-82 in the reply filed on 3/31/2017 is acknowledged.

Claims 71-73, 76-78 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/31/2017.

Claim 79 has been canceled.

Claims 68-70, 74-75, 80-83 are being examined.

Priority

1. The instant application was filed 08/08/2016 is a continuation of 13266862, filed 03/13/2012 and is a national stage entry of PCT/US10/01293 , International Filing Date: 04/30/2010, claims priority from provisional application 61182089, claims priority from provisional application 61179358, filed 05/18/2009, claims priority from provisional application 61178923, filed 05/15/2009, and priority from provisional application 61174470, filed 04/30/2009.

Claim Objections

2. Claims 69, 75, 80, 82 and 83 are objected to because of the following informalities:

Claim 69 depends from claim 68 recites, "wherein said identifying step comprises identifying said differentiator tags." Claim 68 recites, "wherein each differentiator tag is sequenced along with the target nucleic acid molecule to allow each sequencing read to be linked to the target molecule from which it was derived." Thus it is unclear how claim 69 further limits claim 68 as sequencing of the tag appears to identify the differentiator tag.

Claim 75 recites, "said plurality of nucleic acid molecules." Claim 75 depends from claim 68 which recites, "plurality of target nucleic acid molecules." Claims are more concise when the same language is used throughout. Thus the claims should be amended to provide the same language when referencing the nucleic acid molecules.

Claim 80 recites, "said nucleic acid molecules." Claim 80 depends from claim 68 which recites, "plurality of target nucleic acid molecules." Claims are more concise when the same language is used throughout. Thus the claims should be amended to provide the same language when referencing the nucleic acid molecules.

Claim 82 recites, "said plurality of nucleic acid molecules." Claim 82 depends from claim 68 which recites, "plurality of target nucleic acid molecules." Claims are more concise when the same language is used throughout. Thus the claims should be amended to provide the same language when referencing the nucleic acid molecules.

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which

requires, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim 83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags. "It is unclear if the same tag can be used with all locus as long as it is "random" by some standard. The claim should be amended to clarify the relationship.

Appropriate correction is required.

Response to Arguments

This is a new ground of objection necessitated by amendment.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 68-70, 74-75, 80-83 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 68 has been amended to recite, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags." The response .asserts support can be found on page 39, lines 6-20, page 40 lines 10-22 and examples 4-7. Review of the cited portions failed to reveal explicit support for "random locus independent differentiator tags." Further searching the specification revealed recitation random twice with respect to errors, not differentiator tags. Thus the amendment has introduced new matter.

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." The response provides no indication where support for the amendment can be found. Review and searching of the specification did not reveal explicit support for the amendment. Thus the amendment has introduced new matter.

Response to Arguments

This is a new ground of rejection necessitated by amendment.

5. The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 68-70, 74-75, 80-83 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out

and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 68 has been amended to recite, "one or more of a plurality of random locus-independent differentiator tags." "Locus independent differentiator tags" is not an art accepted term. The response .asserts support can be found on page 39, lines 6-20, page 40 lines 10-22 and examples 4-7. Review of the cited portions failed to reveal explicit support for "random locus independent differentiator tags." The specification does not recite the "locus independent differentiator tags." One of skill in the art would not be apprised of what is required of "locus independent differentiator tags" to determine what is inside the scope of the claim and what is not.

Claim 68 has been amended to no longer recite "unique" or "uniquely" in the obtaining and tagging step. However claim 68 still recites, "amplifying said uniquely tagged target nucleic acid molecules to generate amplicons that contain the uniquely tagged target nucleic acid molecule." Thus "said uniquely tagged target" and "the uniquely tagged target" lack antecedent basis in the claim. Thus the metes and bounds are unclear as to what is required of the claim. The claim should be amended to provide antecedent basis for the terms.

Claims 69-70, 74-5, 80-83 are rejected as they depend from claim 68.

Claim 70 recites, "said unique differentiator tags." Claim 70 depends from claim 68, which no longer recites, "unique differentiator tags." Thus it is unclear what differentiator tags the claim is referencing. The claim should be amended to provide antecedent basis for the terms.

Claim Rejections - 35 USC § 102

7. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

8. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim(s) 68-69, 74-75, 81, 83 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10)..

Claim 68 has been amended to recite, ""locus independent differentiator tags." Locus independent differentiator tags" is not an art accepted term. The specification does not recite, "locus independent differentiator tags." Thus the specification does not provide any definition or standard by which to determine what is required of a "locus independent differentiator tags." Thus the broadest reasonable interpretation of "locus independent differentiator tags" is a tag that does not comprise nucleotides of the locus.

With regards to claim 68, Pourmand teaches

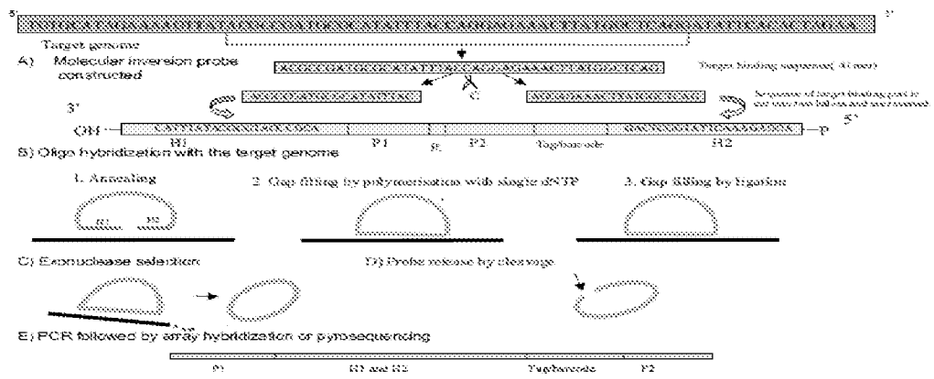

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Pourmand teaches each tag is separate from the target specific sequences and thus is not locus dependent.

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the molecules, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV).

These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which requires, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim 83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags." The

broadest reasonable interpretation is the claims require different differentiator tags for different locus, which is anticipated by the claim.

Response to Arguments

The response traverses the rejection asserting the unique tags of Pourmand are locus dependent. This argument has been thoroughly reviewed but is not considered persuasive as the specification provides no limiting definition of "random locus-independent differentiator tags." Thus the response is providing the representatives assertion of what is required by "random locus-independent differentiator tags."

First, MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.

Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

(1) prior to a final rejection,

(2) before appeal in an application not having a final rejection, or

(3) after final rejection and submitted

(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or

(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37

CFR 1.195, or

(iii) under 37 CFR 1.129(a).

Thus the rejection is maintained.

10. Claim(s) 68-69, 75, 83 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ronaghi (US PGPUB 2006/0008824) .

Claim 68 has been amended to recite, ""locus independent differentiator tags." Locus independent differentiator tags" is not an art accepted term. The specification does not recite, "locus independent differentiator tags." Thus the specification does not provide any definition or standard by which to determine what is required of a "locus independent differentiator tags." Thus the broadest reasonable interpretation of "locus independent differentiator tags" is a tag that does not comprise nucleotides of the locus.

With regards to claim 68, Ronaghi teaches in claim 10 a method of labeling a nucleic acid by use of a unique primer and amplifying. Ronaghi teaches the amplified sequence can be sequenced (claim 10).

Ronaghi teaches, "the unique primer is attached to the nucleic acid molecule by ligating the adapter comprising a unique barcode to the nucleic acid molecule. In further embodiments, the unique barcode comprises a unique sequence of five nucleotides"

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Thus Ronaghi teaches a method of labeling target nucleic acids with a unique primer (or barcode), amplifying and sequencing the amplified sequence, thus identifying the sequence.

With regards to claim 69, Ronaghi teaches sequencing the amplified sequence which would identify the unique differentiator tag.

With regards to claim 75, Ronaghi teaches, "In certain embodiments, the source of nucleic acid is selected from the group consisting of: a BAC clone, a bacterium, and a tissue sample.

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which requires, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim 83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags." The broadest reasonable interpretation is the claims require different differentiator tags for different locus, which is anticipated by the claim.

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(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or

(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37

CFR 1.195, or

(iii) under 37 CFR 1.129(a).

Thus the rejection is maintained.

Claim Rejections - 35 USC § 103

11. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

12. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claim 68-70, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Meyer (Nature Protocols (2008) volume 3, pages 267-278, epublished Jan 31, 2008).

Claim 68 has been amended to recite, ""locus independent differentiator tags." Locus independent differentiator tags" is not an art accepted term. The specification does not recite, "locus independent differentiator tags." Thus the specification does not provide any definition or standard by which to determine what is required of a "locus independent differentiator tags." Thus the broadest reasonable interpretation of "locus independent differentiator tags" is a tag that does not comprise nucleotides of the locus.

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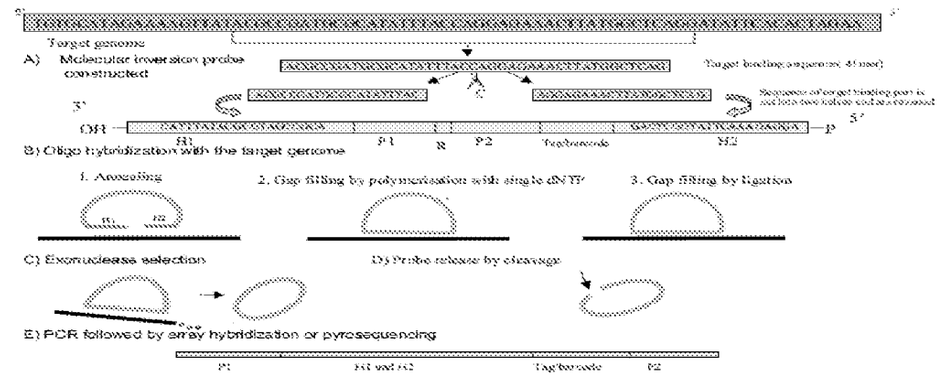

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Pourmand teaches each tag is separate from the target specific sequences and thus is not locus dependent.

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the molecules, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which requires, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim

83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags." The broadest reasonable interpretation is the claims require different differentiator tags for different locus, which is anticipated by the claim.

Poumard does not specifically teach determining presence of sequencing or amplification errors.

However, Meyer teaches preparing batches of barcoded nucleic acids (unique tags) by attaching barcodes or sequence tags to nucleic acids. See p. 271, Box 1; Quality control and Procedure. The barcodes are added to purified PCR products or positive control PCR products (p. 272, Reagent Setup; p. 273, step 10). The batches are pooled and sequenced in parallel. A contamination in a batch of barcodes is determined by determining a frequency at which cross-contamination of adapters occurred during synthesis or dilution. Meyer further teaches a formula that takes into account and estimates false assignment that occurs due to sequencing errors and cross-contamination of barcoding adapters during synthesis and dilution (Box 1). Therefore, Meyer teaches identifying a contamination in a batch of barcodes (unique tags)by determining a frequency at which an incorrect adapter sequence occurs in the batches.

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable

expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis. .

Response to Arguments

The response traverses by asserting the teachings of the Pourmand does not teach all the limitations of the independent claim. This argument has been thoroughly reviewed but is not considered persuasive for the reasons of record.

14. Claim 68-69, 74-75, 80-83 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Shoemaker (US20080090239 published 4/17/2008).

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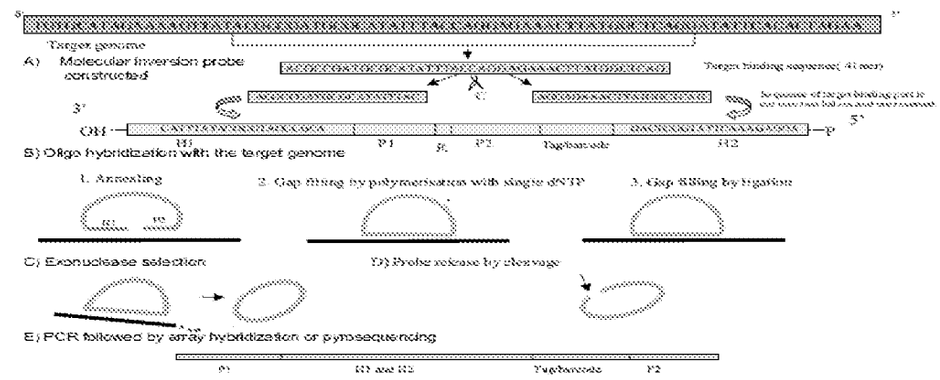

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pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

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Poumard does not specifically teach use of nucleic acids from circulating tumors or fetal nucleic acids.

However, Shoemaker teaches, "[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that

replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large number of maternal cells in the blood which make the analysis time consuming and prone to error."

Shoemaker teaches, "0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying, quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc."

Shoemaker teaches, "In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods, which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of

the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detecting circulating tumor nucleic acids or circulating fetal nucleic acids in the method of Poumard. The artisan would be motivated to use methods that are less invasive methods than aminocentesis or tumor biopsy. The artisan would have a reasonable expectation of success as the artisan is merely using known samples in known methods.

Response to Arguments

The response traverses by asserting the teachings of the Pourmand does not teach all the limitations of the independent claim. This argument has been thoroughly reviewed but is not considered persuasive for the reasons of record.

15. Claim 68-69, 74-75, 80-83 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Ronaghi (US PGPUB 2006/0008824) and Shoemaker (US20080090239 published 4/17/2008).

Claim 68 has been amended to recite, ""locus independent differentiator tags." Locus independent differentiator tags" is not an art accepted term. The specification does not recite, "locus independent differentiator tags." Thus the specification does not provide any definition or standard by which to determine what is required of a "locus independent differentiator tags." Thus the broadest reasonable interpretation of "locus independent differentiator tags" is a tag that does not comprise nucleotides of the locus.

With regards to claim 68, Ronaghi teaches in claim 10 a method of labeling a nucleic acid by use of a unique primer and amplifying. Ronaghi teaches the amplified sequence can be sequenced (claim 10).

Ronaghi teaches, "the unique primer is attached to the nucleic acid molecule by ligating the adapter comprising a unique barcode to the nucleic acid molecule. In further embodiments, the unique barcode comprises a unique sequence of five nucleotides" (007). Ronaghi teaches each tag is separate sequence from the complementary sequence and thus is not locus dependent.

Thus Ronaghi teaches a method of labeling target nucleic acids with a unique primer (or barcode), amplifying and sequencing the amplified sequence, thus identifying the sequence.

With regards to claim 69, Ronaghi teaches sequencing the amplified sequence which would identify the unique differentiator tag.

With regards to claim 75, Ronaghi teaches, "In certain embodiments, the source of nucleic acid is selected from the group consisting of: a BAC clone, a bacterium, and a tissue sample.

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which requires, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim 83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags." The

broadest reasonable interpretation is the claims require different differentiator tags for different locus, which is anticipated by the claim.

Ronaghi does not specifically teach use of nucleic acids from blood sample, circulating tumors or fetal nucleic acids. Rongahi does not specifically teach determining copy number.

However, Shoemaker teaches, "[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large number of maternal cells in the blood which make the analysis time consuming and prone to error."

Shoemaker teaches, "0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying, quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc."

Shoemaker teaches, “In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods, which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes.”

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This is a new ground of rejection.

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Therefore, Meyer teaches identifying a contamination in a batch of barcodes (unique tags)by determining a frequency at which an incorrect adapter sequence occurs in the batches.

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis. .

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This is a new ground of rejection.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*,

686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

18. Claims 68-70, 74-75, 79-82 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No.

13/266,862 in view of Pourmand (BMC informatics (2006) volume 7:500, pages 1-10). This is a provisional nonstatutory double patenting rejection.

Claim 1 of '862 is drawn to A method for analyzing a target nucleic acid, the method comprising: providing a sample comprising a target nucleic acid, contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes (MIPs), each MIP comprising a 5' targeting arm, a central region, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the target nucleic acid, wherein the probe set has a staggered layout such that all of the MIPs capture the target, and some MIPs in the probe set capture additional flanking sequence; converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target nucleic acid; isolating the plurality of circularized probes; and acid sequences of different subregions; and analyzing the isolated subregions.

Claims of '862 do not specifically teach amplifying or a unique barcode.

Claim 68 has been amended to recite, ""locus independent differentiator tags." Locus independent differentiator tags" is not an art accepted term. The specification does not recite, "locus independent differentiator tags." Thus the specification does not provide any definition or standard by which to determine what is required of a "locus independent differentiator tags." Thus the broadest reasonable interpretation of "locus independent differentiator tags" is a tag that does not comprise nucleotides of the locus.

With regards to claim 68, Pourmand teaches

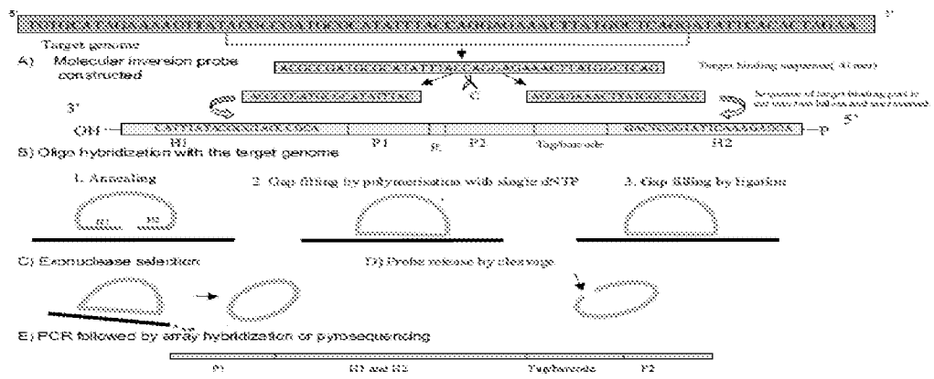

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Pourmand teaches each tag is separate from the target specific sequences and thus is not locus dependent.

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the molecules, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV).

These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which requires, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim 83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags." The

broadest reasonable interpretation is the claims require different differentiator tags for different locus, which is anticipated by the claim.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to improve the molecular inversion probe method of '862 with unique differentiator tags with amplifying and sequencing of Poumard. The artisan would be motivated to amplify and sequence the molecular inversion probes to increase the amount of nucleic acid being detected and thus increase the sensitivity by an art . The artisan would have a reasonable expectation of success as the artisan is merely be using art accepted methods of analysis of nucleic acid sequences using molecular inversion probes.

Response to Arguments

The response request the ODP rejection be held in abeyance. Thus the rejection is maintained.

Summary

No claims are allowed.

Shafer (USPGPUB 2004/0053275) is a reference that may be interest in the instant case.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C POHNERT PhD whose telephone number is (571)272-3803. The examiner can normally be reached on Monday- Friday about 6:00 AM-5:30 PM, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven Pohnert/
Primary Examiner, Art Unit 1634

Notice of References Cited	Application/Control No. 15/231,687	Applicant(s)/Patent Under Reexamination Porreca et al.	
	Examiner STEVEN C POHNERT PhD	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20040053275-A1	03-2004	Shafer, David A.	C07H21/04	435/6.14
	B					
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Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Petitioner Illumina, Inc., EX1003, p. 1156

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/04US 34468/10

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2019-10-24
Name/Print	Thomas C. Meyers	Registration Number	36,989

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

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Filing Date	2016-08-08
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	MLB-002/04US 34468/10

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/SP/	2	9115387		2015-08-25	Umbarger	
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/SP/	1	20040121373	A1	2004-06-24	Friedlander et al.	
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	Attorney Docket Number	MLB-002/04US 34468/10

/SP/	3	20060263789	A1	2006-11-23	Kincaid	
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/SP/	1	2007/061284	WO	A1	2007-05-31	Plant Res Int BV		
/SP/	2	2011066476	WO	A1	2011-06-03	Quantalife, Inc		
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/SP/	3	Meyer, 2008, Parallel tagged sequencing on the 454 platform, Nat Protocol 3(2):267-278	
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	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/04US 34468/10

EXAMINER SIGNATURE			
Examiner Signature	/Steven Pohnert/ (12/17/2019)	Date Considered	12/17/2019

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EFS ID:	38608458
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Sandra Richards
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	18-FEB-2020
Filing Date:	08-AUG-2016
Time Stamp:	15:53:27
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Affidavit-traversing rejectns or objectns rule 132	MLB-002-04US_132-declaration.pdf	32735 c2fd1cea730c47c2d358664c2296be49c875a252	no	4

Warnings:

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2	After Final Consideration Program Request	MLB-002-04US-AFCP-Request.pdf	33151 e80c8cf565d6e722f00fbf990a4de7c8b3555519	no	1
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Multipart Description/PDF files in .zip description

Document Description	Start	End
Response After Final Action	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	9

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Steven Pohnert
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Declaration under 37 C.F.R. §1.132

I, Gregory Porreca, declare as follows:

1. I received a PhD in Genetics from Harvard University and a BS in computer science and biology from The College of New Jersey. I am the Founder, President, and Chief Executive Officer of Molecular Loop Biosolutions, LLC, a company focused on producing on rapid production of sequencer-ready DNA libraries. I have served as a lecturer at Harvard Medical School as well as the Personal Genome Project Director of Technology. I co-developed high-throughput DNA sequencing system technology that is now part of the Applied Biosystems SOLiD nucleic acid sequencing platform. I am a named inventor on more than 30patents or patent applications world-wide. I have authored or co-authored over 14 refereed publications and have presented numerous invited talks and posters on aspects of next-generation-sequencing and medical genetics.

2. I am the inventor of the above captioned patent application. I have reviewed the above-captioned patent application, including the pending claims.

3. I make this declaration in order to present facts known to me and my technical opinion with respect to the above-captioned patent application.

4. The patent application provides preparative and analytical methods for identifying target nucleic acid molecules. *As-filed application,* pg. 6 (lines 20-23); pg. 39 (13-16). The patent application discloses tagging individual nucleic acid molecules with differentiator tags before any amplification or sequencing steps. *Id.*, pg. 6 (21-24); pg. 40 (7-9); pg. 42 (14-27). Each differentiator tag has its own unique sequence so that each individual nucleic acid molecule is tagged, and therefore associated, with its own unique differentiator tag. *Id.,* pg.41 (10-22). Accordingly, each differentiator tag uniquely identifies a single nucleic acid molecule through subsequent amplification and sequencing steps. *Id.,* pg. 39 (21-26); pg. 41 (3-7), (9-10); pg. 42 (13-20). Because each unique differentiator tag is associated with a single nucleic acid molecule, each sequence read can be associated back to its original, individual nucleic acid molecule based

on the unique differentiator tag sequence that has been incorporated into the sequence read. *Id.,* pg. 41 (7-9), (11-12), (23-24); pg. 42 (17-20). The unique combination of individual nucleic acid molecules and their respective unique differentiator tags of the invention correct for bias in subsequent steps. *Id.,* pg. 41 (23) - pg.42 (12). For example, overrepresentation of sequence reads having a combination of a nucleic acid molecule sequence and its unique differentiator tag sequence is indicative of bias in the protocol at one or more steps between the incorporation of the differentiator tag sequence and the sequencing of the combination. *Id.* Accordingly, the bias may be corrected to provide an accurate representation of the individual nucleic acid molecule in the original pool of nucleic acid molecules. *Id.*

5. I have reviewed the Final Office Action mailed December 20, 2019, from the United States Patent and Trademark Office. I understand that the claims pending in the captioned application are alleged to be anticipated by a 2006 BMC Bioinformatics publication by Nader Pourmand, et al., entitled "PathogenMIPer: a tool for the design of molecular inversion proves to detect multiple pathogens" and by United States Pre-Grant Publication No. 2006/0008824 of Mostafa Ronaghi, et al. I also understand that the pending claims are alleged to be obvious over the combined references of Pourmand, Ronaghi, the 2008 Nature Protocols journal article by Matthias Meyer, et al., entitled "Parallel tagged sequencing on the 454 platform", and the United States Published Application No. US20080090239 of Daniel Shoemaker, et. al. I reviewed each of those cited referenced.

6. A distinguishing feature of the claims in my patent application is that each individual nucleic acid molecule is tagged with a unique differentiator tag prior to any amplification or sequencing steps. *As-filed application*, pg. 40 (lines 7-9); pg. 42 (14-27). My claimed methods overcome systematic and random errors in genome capture, amplification, and sequencing. *Id.,* pg. 6 (31-33); pg. 7 (1-4); pg. 28 (1-7); pg. 38 (25-28). In particular, my claimed invention allows for a reduction in errors associated with the capture and amplification of nucleic acids by "collapsing" duplicate sequences, thereby providing a significant improvement in the art. *Id.,* pg. 43 (2-3); pg. 45 (2-6); pg. 80 (11-12); and FIG. 5, final "step".

7. Based on my reading of the Pourmand reference, I understand Pourmand to report a software program for designing molecular inversion probe (MIP) oligonucleotides for use in pathogen identification and detection. *Pourmand,* abstract. Particularly, I understand Pourmand to report MIPs comprised of genomic recognition sequences, common amplification sequences and a molecular barcode for each genotype assigned to a specific gene. *Id.,* pg. 2, col. 1, par. 3. Pourmand states that "[a] universal barcode sequence allows for array detection and quantification of [the] amplified probe." *Id.* (emphasis added). Furthermore, Pourmand reports that the barcodes of the molecular inversion probes are for detection by microarray. *Id.,* pg. 7, col. 1, par. 4.

8. It is my expert option that detection by microarray requires quantitation of an identifier, such as a barcode, to detect the presence of a target molecule. Of necessity, detection of thousands, if not millions, of copies of the same barcode hybridized to the same target molecule is required for Pourmand's reported microarray detection to work. It is my opinion as an expert in the field that for Pourmand to genotype, and thus detect, pathogens by microarray, Pourmand relies on at least thousands of copies of the same barcode to detect the presence of a target. In

contrast, my claims require a unique barcode sequence per each individual target nucleic acid molecule. To that end, it is my expert opinion that if Pourmand were to use a unique barcode per molecule, doing so would render Pourmand inoperative because Pourmand requires the aggregation of the same identifier for detection, which would simply not result if a unique barcode were used per each individual molecule.

9. Based on my reading of the Ronaghi reference, I understand Ronaghi to report using a unique barcode per bacterial artificial chromosome (BAC). *Ronaghi,*(lines 17-21) of [0015]. I understand that Ronaghi states "labelling the nucleic acid molecule with a unique primer" and that a unique primer is reported to contain a unique barcode of 5 nucleotides. *Id.,* (3-4) of [0010]; (4-6) of [0009]. I also understand Ronaghi reports fragmenting a BAC library and saturating all of the fragments with the same unique barcode, resulting in the all of the genomic DNA from one BAC library to carry the same unique barcode. *Id.,*(14-21). I understand that Ronaghi uses a barcode unique to a specific BAC library to distinguish which BAC library clonal amplification products are cloned from in order to ensure sequence assembly of clonal amplification products derived from the same source BAC library. *Id.*, (14-26) of [0015]; [0058].

10. It is my opinion that the "unique" barcodes reported in Ronaghi are only unique to a BAC library for source library identification. Thus, in contrast to the present invention, Ronaghi requires copies of the same barcode for each fragment of a library. Furthermore, for Ronaghi to use a unique barcode per individual fragment produced from a BAC library, doing so would result in amplified sequences that cannot be traced back to the clonal library from which they were generated, thus frustrating the entire purpose of Ronaghi.

11. In my expert opinion it is clear that neither Pourmand nor Ronaghi describe tagging **each individual nucleic acid molecule with a unique barcode** sequence as required by my pending claims.

12. It is my further opinion that the additional references cited in the office action do not alter the methods reported by Pourmand and Rhonagi. For example, Meyer reports a molecular barcoding method for sequencing multiple samples on the 454 platform using sample-specific barcoding adapters. *Meyer*, Abstract (emphasis added). Particularly, Meyer reports parallel tagged sequencing (PTS) that allows for parallel sequencing of a large number of double-stranded DNA (dsDNA) samples on the 454 platform. *Id.,* pg. 267, col. 2, par. 2. Meyer reports achieving PTS by barcoding each sample with a specific tag sequence. *Id.* After pooling the tagged DNA samples, library preparation and sequencing, the tag sequences are used to identify each sequence's sample origin. *Id.*, and pg. 268, col. 1, par. 1. It is my expert opinion that Meyer reports only multiplexing— sequencing multiple samples at the same time. Accordingly, Meyer requires a unique barcode for *all* of the molecules in a sample so all of the sequence reads can be assigned to their sample origin. If Meyer were to use a unique barcode per individual sample molecule doing so would result in amplified sequences that cannot be assigned to their sample origin, thus frustrating the entire purpose of multiplexing and the teaching of Meyer.

13. It is my further opinion that Shoemaker reports labelling one or more regions of genomic DNA in each cell line with a label specific to each cell. *Shoemaker,* (lines 1-5) of [0009]. I understand that Shoemaker uses its unique labels to identify which cell the DNA originates from

in a mixed sample. *Id.,* (5-6) of [0009]. Shoemaker uses the same labels to identify which type of cell the DNA molecules originate from in a mixed sample to identify gene mutations in specific cell types. *Id.,* Abstract. Thus, like the other cited references, if Shoemaker were to use a unique barcode per individual molecule in a mixed sample, doing so would result in amplified sequences that cannot be traced back to any cell type, destroying the purpose of Shoemaker.

14. The assertion that the cited references Pourmand, Ronaghi, Meyer, and Shoemaker teach or suggest the presently claimed method is simply unsupported, as none of the references report tagging individual nucleic acid molecules each with a unique barcode sequence.

15. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: February 18, 2020

/Gregory Porreca/
Gregory Porreca, PhD

63672054 v1

Doc Code: A.NE.AFCP
Document Description: After Final Consideration Pilot Program Request

PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
34468/10US	15/231,687-Conf. #6709	August 8, 2016

First Named Inventor:	Title:
Gregory Porreca	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).

2. The above-identified application contains an outstanding final rejection.

3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.

4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.

5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.

6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).

7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]

8. By filing this certification and request, applicant acknowledges the following:

- Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
- The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
  - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
  - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
    - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
    - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	/Thomas C. Meyers/	Date	February 18, 2020
Name (Print/Typed)	Thomas C. Meyers	Practitioner Registration No.	36,989

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☐ * Total of 1 forms are submitted.

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Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

This paper is in response to a final Office Action mailed December 20, 2019 from the United States Patent and Trademark Office.

Amendments to the claims begin on page 2.

Remarks begin on page 5.

A Declaration under 37 C.F.R. § 1.132 of the Inventor is submitted herewith.

A Certification and Request for Consideration Under the After Final Consideration Pilot Program 2.0 is also submitted herewith.

Applicant believes no fees are due with this paper. Nevertheless, Applicant authorizes any and all required fees due with this response to be charged to Deposit Account No. 50-0369.

Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
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RESPONSE AND AMENDMENT

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AMENDMENTS TO THE CLAIMS

Please amend the claims as follows. The following listing of claims will replace all prior versions of claims in the application.

1-67. (Canceled)

68. (Currently Amended) A method for nucleic acid identification, the method comprising the steps of:

obtaining a biological sample comprising a plurality of target nucleic acid molecules;

tagging each of the plurality of target nucleic acid molecules ~~from the biological sample~~ with a unique ~~one or more of a plurality of random locus-independent~~ differentiator tag[[s]], thereby generating a plurality of uniquely tagged target nucleic acid molecule[[s]]~~, the differentiator tags remaining attached to the target nucleic acid molecules through amplification and sequencing steps to allow unique identification of each target nucleic acid molecule~~;

amplifying each of the plurality of ~~said~~ uniquely tagged target nucleic acid molecules to generate amplicons of each ~~that contain the~~ uniquely tagged target nucleic acid molecule[[s]];

~~identifying the target nucleic acid molecule by~~ sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence; and ~~differentiator tag is sequenced along with the target nucleic acid molecule to allow each sequencing read to be linked to the target molecule from which it was derived~~

identifying said target nucleic acid molecule sequences based on the differentiator tag sequence of each of the sequence reads.

69. (Currently Amended) The method of claim 68, wherein said identifying step further comprises identifying independent target nucleic acid molecule sequences based on unique [[said]] differentiator tag[[s]] sequences in each of the sequence reads.

70. (Currently Amended) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon [[the]] a number of said unique differentiator tag[[s]] sequences.

71. (Withdrawn) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

72. (Withdrawn) The method of claim 71, wherein said common identifier is used to identify a sample source.

73. (Withdrawn) The method of claim 72, wherein said common identifier is used to identify a patient.

74. (Previously Presented) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (Currently Amended) The method of claim 68, wherein said plurality of target nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (Withdrawn) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

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77. (Withdrawn) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

78. (Withdrawn) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

79. (Canceled)

80. (Currently Amended) The method of claim 68, wherein said plurality of target nucleic acid molecules are circulating tumor nucleic acid molecules.

81. (Previously Presented) The method of claim 68, further comprising the step of determining the copy number of a genomic region or transcript in a patient from whom the sample is obtained.

82. (Currently Amended) The method of claim 68, wherein said plurality of target nucleic acid molecules are maternally-circulating fetal or placental nucleic acid molecules.

83. (Canceled)

Remarks

Claims 68-78 and 80-82 are pending in the application. Claims 68 - 70, 75, 80, and 82 are currently amended. Support for the claim amendments is found throughout the as-filed application, for example at page 6 (lines 21-24), page 39 (21-26), page 40 (7-9), page 41 (3-22) and page 42 (lines 13-27). No new matter is added.

Claim Objections

The Office Action, at page 3, states claims 69, 75, 80, 82, and 83 are objected to for informalities. Applicant has amended claims 69, 75, 80, 82, and 83 as suggested by the Examiner. The objections are believed to be overcome.

Rejections under 35 U.S.C. §112

The Office Action, at page 4, states that claims 68-70, 74-75, and 80-83 are rejected under 35 U.S.C. §112(a) for failing to comply with the written description requirement. The Office Action, at page 5, states that claims 68-70, 74-75, and 80-83 are rejected under 35 U.S.C. §112(b) as being indefinite. Without acquiescing to the propriety of the rejection, and in the interest of advancing this case to allowance, Applicant has amended independent claim 68 to address the written description rejection and the indefiniteness rejection. In light of the amendment, Applicant respectfully requests withdrawal of these rejections.

Prior Art Rejections

The Office Action, at page 7, states that claims 68-69, 74-75, 81, and 83 are rejected under 35 U.S.C. §102(b) over Pourmand, et al. (BMC Informatics (2006) volume 7:500, pages 1-10). The Office Action, at page 11, states that claims 68-69, 75, and 83 are rejected under 35 U.S.C. §102(b) over US PGPUB 2006/0008824 of Ronaghi. The Office Action, at page 14, states claims 68-70, 74-75, and 81 are rejected under 35 U.S.C. §103(a) over Pourmand and

Meyer, et al. (Nature Protocols (2008) volume 3, pages 267-278, epublished January 31, 2008); at page 22, that claims 68-69, 74-75, and 80-83 over Ronaghi and US20080090239 of Shoemaker; and at page 26, that claims 68-70, 74-75, and 81 over Ronaghi and Meyer.

In order to anticipate a claim, the Patent Office requires that a reference show each and every element of the claim. MPEP §2131. In order to establish a *prima facie* case of obviousness, there must be a suggestion in the cited art to modify a reference or to combine multiple references in a manner that would lead one of ordinary skill in the art to an applicant's claimed invention. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Particularly, the Examiner concludes that both Pourmand and Ronaghi teach a method of labeling target nucleic acids with a unique barcode, amplifying and sequencing the amplified sequence, thus identifying the sequence. *Office Action*, pg. 8 and pg. 12, respectively. Applicant respectfully disagrees with Examiner's maintained and unsupported conclusory statements. Applicant reminds the Examiner that the Office must provide evidence to substantiate technical conclusions or, if the Examiner is a subject matter expert, he or she should provide an affidavit providing evidence of expertise and the technical basis for the conclusions made. *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); *see also KSR Int'l Co. v. Teleflex Inc*, 550 U.S. 398, 418, 82 USPQ2d at 1396.

As amended, independent claim 68 requires tagging <u>each</u> of a plurality of target nucleic acid molecules with a <u>unique</u> differentiator tag to generate a plurality of uniquely tagged target nucleic acid molecules. Applicant submits that element is wholly missing from the cited references and provides a declaration of the inventor, Dr. Gregory Porreca, providing his expert opinion to that effect.

Applicant developed preparative and analytical methods for identifying target nucleic acid molecules that account for systematic and random errors in genome capture, amplification, and sequencing. *Porreca dec., par. 6.* Applicant's claimed method requires that **each individual nucleic acid molecule is tagged with a unique differentiator tag** prior to any amplification or

sequencing steps. *Id.* (emphasis added). Dr. Porreca concludes that each of Pourmand, Ronaghi, Meyer, and Shoemaker fail to describe tagging each individual nucleic acid molecule with a unique barcode sequence as required by the pending claims. *Id., par. 11 and 12.*

Pourmand reports a **universal barcode sequence** that allows for array detection and quantification of the amplified probe. *Pourmand*, pg. 2, col. 1, par. 3. (emphasis added). Pourmand reports using its universal barcode sequence for pathogen identification and detection. *Id.,* abstract. Accordingly, Pourmand relies on at least thousands of copies of the **same** barcode hybridized to the same target molecule to genotype and thus detect pathogens by microarray. *Porreca dec., par. 8.* In contrast, the present claims require a **unique** barcode sequence per each individual target nucleic acid molecule, which is wholly missing from Pourmand. If Pourmand modified its teaching to use a unique barcode per molecule instead of the same barcode, doing so would frustrate the ability to detect the type of pathogen by microarray because aggregation of the same barcode could simply not occur. *Id.*

Ronaghi reports using a barcode unique to a specific BAC library to distinguish which BAC library clonal amplification products are cloned from in order to ensure sequence assembly of clonal amplification products derived from the same source BAC library. *Ronaghi*, (lines 14-26) of [0015]; [0058]. The "unique" barcodes reported in Ronaghi are unique only to all of the fragments coming from a BAC library for source library identification. Thus, in contrast to the present invention, Ronaghi requires copies of the **same barcode** for each fragment coming from the same library. *Porreca dec., par. 10* (emphasis added). If Ronaghi modified its teaching to use a unique barcode per individual fragment produced from a BAC library, doing so would result in amplified sequences that cannot be traced back to the clonal library from which they were generated, thus destroying Ronaghi's entire purpose.

Applicant submits that the secondary references of Meyer and Shoemaker do not make up for what Pourmand and Ronaghi lack.

Meyer reports achieving parallel tagged sequencing by barcoding each sample with a specific tag sequence. *Meyer,* pg. 267, col. 2, par. 2. Since Meyer reports multiplexing, Meyer requires a unique barcode for all of the molecules in a sample so all of the sequence reads can be assigned to their sample origin. *Porreca, dec. par. 12.* Accordingly, Meyer provides a method for solving for sample identification when multiple patient samples are mixed together and being amplified and sequenced. Even if there was some motivation to modify Meyer itself to use a unique barcode per individual sample molecule, doing so would result in amplified sequences that cannot be assigned to their sample origin, frustrating its entire purpose. Thus, even if combined with either Pourmand or Ronaghi, the combinations all fail to arrive at the presently claimed unique barcode per molecule.

Shoemaker reports using unique labels to identify which cell DNA originates from in a mixed sample. *Shoemaker*, (lines 5-6) of [0009]. Shoemaker uses the **same** labels to identify which type of cell the DNA molecules originate from in a mixed sample to identify gene mutations in specific cell types. *Porreca, dec., par.13.* Even if Shoemaker were modified to use a unique barcode per individual molecule in a mixed sample, doing so would destroy the ability to trace amplified sequences back to their originating cell type. *Id.* Like Meyer, even if Shoemaker were combined with either Pourmand or Ronaghi, the combinations all fail to arrive at the presently claimed unique barcode per molecule.

Applicant respectfully submits that the amended claims clarify that individual nucleic acid molecules are each tagged with a unique barcode sequence, and, as discussed above, no combination of the cited references teach or suggest that element of the claims. Since that element is missing from all of the cited references, it would be improper to maintain the prior art rejections.

Applicant believes the rejections under §§102 and 103 are addressed and overcome.

Double Patenting

Claims 68-70, 74, 75, and 79-82 are provisionally rejected on the ground of nonstatutory double patenting over claim 1 of co-pending Application No. 13/266,862 in view of Pourmand.

Applicant believes submission of a Terminal Disclaimer for the above referenced application at this time would be premature. Applicant will address the above referenced application the application is deemed allowable. Applicant believes the double patenting rejection is addressed.

Summary

Applicant respectfully submits that the presently amended claims are in condition for allowance, which is respectfully requested. If there are any questions regarding the above remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: February 18, 2020

Respectfully submitted,
BROWN RUDNICK LLP

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63672053 v1

Petitioner Illumina, Inc., EX1003, p. 1179

Examiner-Initiated Interview Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA (FITF) Status** No

All participants (applicant, applicant's representative, PTO personnel):

(1) STEVEN C. POHNERT PhD. (3) _____.

(2) Thomas Meyere. (4) _____.

Date of Interview: 26 February 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☑ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 68.

Identification of prior art discussed: cited.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The examiner contacted the representative to indicate in view of the extensive amendment to the claims the response could not be reviewed in the time allotted under AFCP2.0. The examiner indicated the amendment would not be entered and we be treated under pre-pilot practices. No discussion of patentability occurred..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Steven Pohnert/
Primary Examiner, Art Unit 1634

Petitioner Illumina, Inc., EX1003, p. 1180

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 03/02/2020

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/02/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA (FITF) Status** No

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 February 2020 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

NO NOTICE OF APPEAL FILED

1. ☑ The reply was filed after a final rejection. No Notice of Appeal has been filed. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114 if this is a utility or plant application. Note that RCEs are not permitted in design applications. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires ____ months from the mailing date of the final rejection.
   b) ☑ The period for reply expires on: (1) the mailing date of this Advisory Action; or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   c) ☐ A prior Advisory Action was mailed more than 3 months after the mailing date of the final rejection in response to a first after-final reply filed within 2 months of the mailing date of the final rejection.The current period for reply expires ____ months from the mailing date of *the prior Advisory Action* or SIX MONTHS from the mailing date of the final rejection, whichever is earlier.
   Examiner Note: If box 1 is checked, check either box (a), (b) or (c). ONLY CHECK BOX (b) WHEN THIS ADVISORY ACTION IS THE FIRST RESPONSE TO APPLICANTS FIRST AFTER-FINAL REPLY WHICH WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. ONLY CHECK BOX (c) IN THE LIMITED SITUATION SET FORTH UNDER BOX (c). See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) or (c) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37CFR 41.37(a).

AMENDMENTS

3. ☑ The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   a) ☑ They raise new issues that would require further consideration and/or search (see NOTE below);
   b) ☐ They raise the issue of new matter (see NOTE below);
   c) ☑ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: See continuation sheet (See 37CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicants reply has overcome the following rejection(s): _____
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☑ For purposes of appeal, the proposed amendment(s):(a) ☑ will not be entered, or (b) ☐ will be entered, and an explanation of how the new or amended claims would be rejected is provided below or appended.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____
9. ☐ The affidavit or other evidence filed after final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
10. ☑ The affidavit or other evidence filed after the date of filing the Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
11. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

12. ☑ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation sheet.
13. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
14. ☑ Other: 2323, 413B.

STATUS OF CLAIMS

15. The status of the claim(s) is (or will be) as follows:
    Claim(s) allowed:_____.
    Claim(s) objected to:See Continuation Sheet.
    Claim(s) rejected:68-70,74-75 and 80-83.
    Claim(s) withdrawn from consideration:71-73 and 76-78.

/Steven Pohnert/
Primary Examiner, Art Unit 1634

Petitioner Illumina, Inc., EX1003, p. 1182

Continuation of STATUS OF CLAIMS 15. Claim(s) objected to: 68-70,74-75 and 80-83

Attachment to Advisory

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

AFCP2.0

Applicant's request for entry into AFCP 2.0 is acknowledged, but is denied because the response cannot be reviewed and a search conducted in the limited amount of time authorized for this pilot program. Therefore, the response is being reviewed under pre-pilot practice.

Continuation of box 3: The amendments filed on 2/18 further limit the claims to, "tagging each of the plurality of target nucleic acid molecules ~~from the biological sample~~ with a unique ~~one or more of a plurality of random locus independent~~ differentiator tag[[s]], thereby generating a plurality of uniquely tagged target nucleic acid molecule[[s]]~~, the differentiator tags remaining attached to the target nucleic acid molecules through amplification and sequencing steps to allow unique identification of each target nucleic acid molecule~~; amplifying each of the plurality of ~~said~~ uniquely tagged target nucleic acid molecules to generate amplicons of each ~~that contain the~~ uniquely tagged target nucleic acid molecule[[s]]; ~~identifying the target nucleic acid molecule by~~ sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence; and ~~differentiator tag is sequenced along with the target nucleic acid molecule to allow each sequencing read to be linked to the target molecule from which it was~~

~~derived~~ identifying said target nucleic acid molecule sequences based on the differentiator tag sequence of each of the sequence reads.." These new limitations further limit the scope of the claims and thus require further search and consideration because the claims now require additional elements not present at time of final rejection.

MPEP 714.13 states, " It should be kept in mind that applicant cannot, as a matter of right, amend any finally rejected claims, add new claims after a final rejection (see 37 CFR 1.116) or reinstate previously canceled claims. Except where an amendment merely cancels claims, adopts examiner suggestions, removes issues for appeal, or in some other way requires only a cursory review by the examiner, compliance with the requirement of a showing under 37 CFR 1.116(b)(3) is expected in all amendments after final rejection."

The newly amended claims require, "tagging each of the plurality of target nucleic acid molecules ~~from the biological sample~~ with a unique ~~one or more of a plurality of random locus independent~~ differentiator tag[[s]], thereby generating a plurality of uniquely tagged target nucleic acid molecule[[s]]~~, the differentiator tags remaining attached to the target nucleic acid molecules through amplification and sequencing steps to allow unique identification of each target nucleic acid molecule~~; amplifying each of the plurality of ~~said~~ uniquely tagged target nucleic acid molecules to generate amplicons of each ~~that contain the~~ uniquely tagged target nucleic acid molecule[[s]]; ~~identifying the target nucleic acid molecule by~~ sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a

differentiator tag sequence; and ~~differentiator tag is sequenced along with the target nucleic acid molecule to allow each sequencing read to be linked to the target molecule from which it was derived~~ identifying said target nucleic acid molecule sequences based on the differentiator tag sequence of each of the sequence reads.. This is a new limitation that has not previously been present at the time of final rejection and thus would require a new search.

Continuation of box 12:

After final rejection, applicant is entitled to nothing more than cursory review unless the after-final reply merely cancels claims, adopts examiner suggestions, or removes issues for appeal. M.P.E.P. § 714.13, part II.

The response traverse the 112 rejections in view of the amendment. This argument is not persuasive in view of the non-entry of the amendment.

The response traverses the 103 rejection in view of the amendment and declaration from Porreca. This argument has been thoroughly reviewed but is not considered in view of the non-entry of the amendment and declaration as the response has provides no sufficient reasons the declaration could not be provided earlier. The Pourmand reference has been of record since 6/6/2017.

The response continues by providing arguments the art does not teach the limitations of the amended claims. This argument is not persuasive in view of the amendment not being entered.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C POHNERT PhD whose telephone number is (571)272-3803. The examiner can normally be reached on Monday- Friday about 6:00 AM-5:30 PM, every second Friday off, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-07311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven Pohnert/
Primary Examiner, Art Unit 1634

do not enter amendments

/SP/

Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

This paper is in response to a final Office Action mailed December 20, 2019 from the United States Patent and Trademark Office.

Amendments to the claims begin on page 2.

Remarks begin on page 5.

A Declaration under 37 C.F.R. § 1.132 of the Inventor is submitted herewith.

A Certification and Request for Consideration Under the After Final Consideration Pilot Program 2.0 is also submitted herewith.

Applicant believes no fees are due with this paper. Nevertheless, Applicant authorizes any and all required fees due with this response to be charged to Deposit Account No. 50-0369.

AFCP 2.0 Decision	Application No.	Applicant(s)	
	15/231,687	Porreca et al.	
	Examiner	Art Unit	AIA (FITF) Status
	STEVEN C POHNERT PhD	1634	No

This is in response to the After Final Consideration Pilot request filed 18 February 2020.

1. **Improper Request** – The AFCP 2.0 request is improper for the following reason(s) and the after final amendment submitted with the request will be treated under pre-pilot procedure.

   ☐ An AFCP 2.0 request form PTO/SB/434 (or equivalent document) was not submitted.

   ☐ A non-broadening amendment to at least one independent claim was not submitted.

   ☐ The request is not the first proper AFCP 2.0 request submitted in response to the most recent final rejection.

   ☐ Other: _____

2. **Proper Request**

   A. After final amendment submitted with the request will not be treated under AFCP 2.0.
   The after final amendment cannot be reviewed and a search conducted within the guidelines of the pilot program.

   ☑ The after final amendment will be treated under pre-pilot procedure.

   B. Updated search and/or completed additional consideration.
   The examiner performed an updated search and/or completed additional consideration of the after final amendment within the time authorized for the pilot program. The result(s) of the updated search and/or completed additional consideration are:

   ☐ 1. All of the rejections in the most recent final Office action are overcome and a Notice of Allowance is issued herewith.

   ☐ 2. The after final amendment would not overcome all of the rejections in the most recent final Office action . See attached interview summary for further details.

   ☐ 3. The after final amendment was reviewed, and it raises a new issue(s). See attached interview summary for further details.

   ☐ 4. The after final amendment raises new issues, but would overcome all of the rejections in the most recent final Office action. A decision on determining allowability could not be made within the guidelines of the pilot. See attached interview summary for further details, including any newly discovered prior art.

   ☐ 5. Other: _____

   Examiner Note: Please attach an interview summary when necessary as described above.

Petitioner Illumina, Inc., EX1003, p. 1189

Electronic Acknowledgement Receipt	
EFS ID:	38849238
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Thomas Hellenthal
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	12-MAR-2020
Filing Date:	08-AUG-2016
Time Stamp:	16:20:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$950
RAM confirmation Number	E20203BG21034948
Deposit Account	500369
Authorized User	Thomas Hellenthal

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Affidavit-traversing rejectns or objectns rule 132	MLB-002-04US_132-declaration.pdf	32735 c2fd1cea730c47c2d358664c2296be49c875a252	no	4
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	34468_10US_RCE_FillablePDF.pdf	1397049 26b3e21eb78727f5363a0d7d28e8510f9802aa82	no	3
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30660 0c4e008732c2e3499e8f0f0e08327bfa547a0d58	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1460444		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Steven Pohnert
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Declaration under 37 C.F.R. §1.132

I, Gregory Porreca, declare as follows:

1. I received a PhD in Genetics from Harvard University and a BS in computer science and biology from The College of New Jersey. I am the Founder, President, and Chief Executive Officer of Molecular Loop Biosolutions, LLC, a company focused on producing on rapid production of sequencer-ready DNA libraries. I have served as a lecturer at Harvard Medical School as well as the Personal Genome Project Director of Technology. I co-developed high-throughput DNA sequencing system technology that is now part of the Applied Biosystems SOLiD nucleic acid sequencing platform. I am a named inventor on more than 30patents or patent applications world-wide. I have authored or co-authored over 14 refereed publications and have presented numerous invited talks and posters on aspects of next-generation-sequencing and medical genetics.

2. I am the inventor of the above captioned patent application. I have reviewed the above-captioned patent application, including the pending claims.

3. I make this declaration in order to present facts known to me and my technical opinion with respect to the above-captioned patent application.

4. The patent application provides preparative and analytical methods for identifying target nucleic acid molecules. *As-filed application,* pg. 6 (lines 20-23); pg. 39 (13-16). The patent application discloses tagging individual nucleic acid molecules with differentiator tags before any amplification or sequencing steps. *Id.*, pg. 6 (21-24); pg. 40 (7-9); pg. 42 (14-27). Each differentiator tag has its own unique sequence so that each individual nucleic acid molecule is tagged, and therefore associated, with its own unique differentiator tag. *Id.,* pg.41 (10-22). Accordingly, each differentiator tag uniquely identifies a single nucleic acid molecule through subsequent amplification and sequencing steps. *Id.,* pg. 39 (21-26); pg. 41 (3-7), (9-10); pg. 42 (13-20). Because each unique differentiator tag is associated with a single nucleic acid molecule, each sequence read can be associated back to its original, individual nucleic acid molecule based

on the unique differentiator tag sequence that has been incorporated into the sequence read. *Id.,* pg. 41 (7-9), (11-12), (23-24); pg. 42 (17-20). The unique combination of individual nucleic acid molecules and their respective unique differentiator tags of the invention correct for bias in subsequent steps. *Id.,* pg. 41 (23) - pg.42 (12). For example, overrepresentation of sequence reads having a combination of a nucleic acid molecule sequence and its unique differentiator tag sequence is indicative of bias in the protocol at one or more steps between the incorporation of the differentiator tag sequence and the sequencing of the combination. *Id.* Accordingly, the bias may be corrected to provide an accurate representation of the individual nucleic acid molecule in the original pool of nucleic acid molecules. *Id.*

5. I have reviewed the Final Office Action mailed December 20, 2019, from the United States Patent and Trademark Office. I understand that the claims pending in the captioned application are alleged to be anticipated by a 2006 BMC Bioinformatics publication by Nader Pourmand, et al., entitled "PathogenMIPer: a tool for the design of molecular inversion proves to detect multiple pathogens" and by United States Pre-Grant Publication No. 2006/0008824 of Mostafa Ronaghi, et al. I also understand that the pending claims are alleged to be obvious over the combined references of Pourmand, Ronaghi, the 2008 Nature Protocols journal article by Matthias Meyer, et al., entitled "Parallel tagged sequencing on the 454 platform", and the United States Published Application No. US20080090239 of Daniel Shoemaker, et. al. I reviewed each of those cited referenced.

6. A distinguishing feature of the claims in my patent application is that each individual nucleic acid molecule is tagged with a unique differentiator tag prior to any amplification or sequencing steps. *As-filed application*, pg. 40 (lines 7-9); pg. 42 (14-27). My claimed methods overcome systematic and random errors in genome capture, amplification, and sequencing. *Id.,* pg. 6 (31-33); pg. 7 (1-4); pg. 28 (1-7); pg. 38 (25-28). In particular, my claimed invention allows for a reduction in errors associated with the capture and amplification of nucleic acids by "collapsing" duplicate sequences, thereby providing a significant improvement in the art. *Id.,* pg. 43 (2-3); pg. 45 (2-6); pg. 80 (11-12); and FIG. 5, final "step".

7. Based on my reading of the Pourmand reference, I understand Pourmand to report a software program for designing molecular inversion probe (MIP) oligonucleotides for use in pathogen identification and detection. *Pourmand,* abstract. Particularly, I understand Pourmand to report MIPs comprised of genomic recognition sequences, common amplification sequences and a molecular barcode for each genotype assigned to a specific gene. *Id.,* pg. 2, col. 1, par. 3. Pourmand states that "[a] universal barcode sequence allows for array detection and quantification of [the] amplified probe." *Id.* (emphasis added). Furthermore, Pourmand reports that the barcodes of the molecular inversion probes are for detection by microarray. *Id.,* pg. 7, col. 1, par. 4.

8. It is my expert option that detection by microarray requires quantitation of an identifier, such as a barcode, to detect the presence of a target molecule. Of necessity, detection of thousands, if not millions, of copies of the same barcode hybridized to the same target molecule is required for Pourmand's reported microarray detection to work. It is my opinion as an expert in the field that for Pourmand to genotype, and thus detect, pathogens by microarray, Pourmand relies on at least thousands of copies of the same barcode to detect the presence of a target. In

contrast, my claims require a unique barcode sequence per each individual target nucleic acid molecule. To that end, it is my expert opinion that if Pourmand were to use a unique barcode per molecule, doing so would render Pourmand inoperative because Pourmand requires the aggregation of the same identifier for detection, which would simply not result if a unique barcode were used per each individual molecule.

9. Based on my reading of the Ronaghi reference, I understand Ronaghi to report using a unique barcode per bacterial artificial chromosome (BAC). *Ronaghi,*(lines 17-21) of [0015]. I understand that Ronaghi states "labelling the nucleic acid molecule with a unique primer" and that a unique primer is reported to contain a unique barcode of 5 nucleotides. *Id.,* (3-4) of [0010]; (4-6) of [0009]. I also understand Ronaghi reports fragmenting a BAC library and saturating all of the fragments with the same unique barcode, resulting in the all of the genomic DNA from one BAC library to carry the same unique barcode. *Id.,*(14-21). I understand that Ronaghi uses a barcode unique to a specific BAC library to distinguish which BAC library clonal amplification products are cloned from in order to ensure sequence assembly of clonal amplification products derived from the same source BAC library. *Id.*, (14-26) of [0015]; [0058].

10. It is my opinion that the "unique" barcodes reported in Ronaghi are only unique to a BAC library for source library identification. Thus, in contrast to the present invention, Ronaghi requires copies of the same barcode for each fragment of a library. Furthermore, for Ronaghi to use a unique barcode per individual fragment produced from a BAC library, doing so would result in amplified sequences that cannot be traced back to the clonal library from which they were generated, thus frustrating the entire purpose of Ronaghi.

11. In my expert opinion it is clear that neither Pourmand nor Ronaghi describe tagging **each individual nucleic acid molecule with a unique barcode** sequence as required by my pending claims.

12. It is my further opinion that the additional references cited in the office action do not alter the methods reported by Pourmand and Rhonagi. For example, Meyer reports a molecular barcoding method for sequencing multiple samples on the 454 platform using sample-specific barcoding adapters. *Meyer*, Abstract (emphasis added). Particularly, Meyer reports parallel tagged sequencing (PTS) that allows for parallel sequencing of a large number of double-stranded DNA (dsDNA) samples on the 454 platform. *Id.,* pg. 267, col. 2, par. 2. Meyer reports achieving PTS by barcoding each sample with a specific tag sequence. *Id.* After pooling the tagged DNA samples, library preparation and sequencing, the tag sequences are used to identify each sequence's sample origin. *Id.*, and pg. 268, col. 1, par. 1. It is my expert opinion that Meyer reports only multiplexing— sequencing multiple samples at the same time. Accordingly, Meyer requires a unique barcode for *all* of the molecules in a sample so all of the sequence reads can be assigned to their sample origin. If Meyer were to use a unique barcode per individual sample molecule doing so would result in amplified sequences that cannot be assigned to their sample origin, thus frustrating the entire purpose of multiplexing and the teaching of Meyer.

13. It is my further opinion that Shoemaker reports labelling one or more regions of genomic DNA in each cell line with a label specific to each cell. *Shoemaker,* (lines 1-5) of [0009]. I understand that Shoemaker uses its unique labels to identify which cell the DNA originates from

in a mixed sample. *Id.,* (5-6) of [0009]. Shoemaker uses the same labels to identify which type of cell the DNA molecules originate from in a mixed sample to identify gene mutations in specific cell types. *Id.,* Abstract. Thus, like the other cited references, if Shoemaker were to use a unique barcode per individual molecule in a mixed sample, doing so would result in amplified sequences that cannot be traced back to any cell type, destroying the purpose of Shoemaker.

14. The assertion that the cited references Pourmand, Ronaghi, Meyer, and Shoemaker teach or suggest the presently claimed method is simply unsupported, as none of the references report tagging individual nucleic acid molecules each with a unique barcode sequence.

15. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: February 18, 2020

/Gregory Porreca/
Gregory Porreca, PhD

63672054 v1

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	15231687	Filing Date	2016-08-08	Docket Number (if applicable)	MLB-002/04US 34468/10	Art Unit	1634
First Named Inventor	Gregory Porreca			Examiner Name	S. C. Pohnert		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☒ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☐ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☒ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 50-0369

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

Applicant Signature

EFS - Web 2.1.16

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2020-03-12
Name	Thomas C. Meyers	Registration Number	36989

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal	
Application Number:	15231687
Filing Date:	08-Aug-2016
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Thomas Hellenthal
Attorney Docket Number:	MLB-002/04US 34468/10

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	950	950
		Total in USD ($)		**950**

Electronic Acknowledgement Receipt

EFS ID:	39840653
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Kelley Warren
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	26-JUN-2020
Filing Date:	08-AUG-2016
Time Stamp:	15:28:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	Information_Disclosure_Statement.pdf	19203 3e35df3a2c892c7136830b5c2e370f6e43993b32	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	34468_10US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1034646 9b9135c8f177dd247ff69938f66ccaaa548d0f78	no	4
Warnings:					
Information:					
3	Non Patent Literature	34468_10US_-_Abravaya-1995.pdf	828901 21f96e72fc479cf053530bab555d54e0a7a5ece4	no	8
Warnings:					
Information:					
4	Non Patent Literature	34468_9US_-_Bhangale-2006-NatGenet.pdf	791203 9e59f3ce91d60781b528ef8b6e024e5b900262bf	no	6
Warnings:					
Information:					
5	Non Patent Literature	34468_10US_-_FOA_US13266862.pdf	1455033 26b93d4249bdfcd89bc61e4fb78277f09f681b8b	no	33
Warnings:					
Information:					
6	Non Patent Literature	34468_10US_-_Meriam_Webster-_Stagger.pdf	363861 49548872ed40ce3b8ce5abc563a2fb189343a27d	no	9
Warnings:					
Information:					
		Total Files Size (in bytes):	4492847		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: MLB-002/04US
34468/10
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Molecular Loop Biosolutions, LLC

Application No.: 15/231,687 | Confirmation No.: 6709

Filed: August 8, 2016 | Art Unit: 1634

For: METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS | Examiner: S. C. Pohnert

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT (IDS)

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114 (37 C.F.R. § 1.97(b)(4)).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

63802449

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Dated: June 26, 2020

Respectfully submitted,

Electronic signature: /Thomas C. Meyers/
Thomas C. Meyers
Registration No.: 36,989
BROWN RUDNICK LLP
Brown Rudnick LLP
One Financial Center
Boston, Massachusetts 02111
(617) 856-8200
Attorney for Applicant

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/04US 34468/10

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2020-06-26
Name/Print	Thomas C. Meyers	Registration Number	36,989

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15231687
Filing Date	2016-08-08
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	MLB-002/04US 34468/10

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	10202637		2019-02-12	Umbarger	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20040053275	A1	2004-03-18	Shafer	
	2	20050250147	A1	2005-11-10	Macevicz	

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FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

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NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/04US 34468/10

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Abravaya, 1995, Detection of point mutations with a modified ligase chain reaction (Gap-LCR), Nucleic Acids Research, 23(4): 675-682	
	2	Bhangale, 2006, Automating resequencing-based detection of insertion-deletion polymorphisms, Nature Genetics 38:1457-1462	
	3	Final Rejection issued in U.S. Application No. 13/266,862, date of mailing: June 9, 2020, 33 pages	
	4	Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign_sd&utm_medium=serp&utm_source=jsonld), downloaded June 3, 2020, 9 pages	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 07/14/2020

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
07/14/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Office Action Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA (FITF) Status** No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 3/12/2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 68-78 and 80-82 is/are pending in the application.

5a) Of the above claim(s) 71-73 and 76-78 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68-70,74-75 and 80-82 is/are rejected.

8) ☑ Claim(s) 69 is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 10/21/2016 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Petitioner Illumina, Inc., EX1003, p. 1211

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/12/2020 has been entered.

Claim Status and Formal matters

This action is in response to papers filed 3/12/2020.

Claims 68-78, 80-82 are pending.

Claims 68-70, 80, 82 have been amended.

Applicant's election without traverse of group I, claims 68-70, 74-75, 80-82 in the reply filed on 3/31/2017 is acknowledged.

Claims 71-73, 76-78 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/31/2017.

Claim 79 has been canceled.

Claims 68-70, 74-75, 80-82 are being examined.

The previous 112(a) and 112(b) rejections have been withdrawn in view of the amendments to delete the issues of record.

Response to Amendment

2. The declaration under 37 CFR 1.132 filed 3/12/2020 is insufficient to overcome the rejection of claims 68-70, 74-75, 80-82 based upon Pourmand and Ronaghi as set forth in the last Office action because: The declaration is by the inventor of the instant application had thus has a vested interest in the outcome of the application.

The declaration asserts, " Each differentiator tag has its own unique sequence so that each individual nucleic acid molecule is tagged, and therefore associated, with its own unique differentiator tag. *Id.*, pg.41 (10-22). Accordingly, each differentiator tag uniquely identifies a single nucleic acid molecule through subsequent amplification and sequencing steps. *Id.*, pg. 39 (21-26); pg. 41 (3-7), (9-10); pg. 42 (13-20). Because each unique differentiator tag is associated with a single nucleic acid molecule, each sequence read can be associated back to its original, individual nucleic acid molecule based." This argument has been thoroughly reviewed but is not considered persuasive as the declaration is attempting to assert each nucleic has its own unique tag. However the claim requires tagging a plurality of target nucleic acid molecules with a unique tag, which encompass a single unique tag which is same but unique on all target molecules.

The declaration in section 4 asserts this can be used to correct for bias. However, the specification teaches on page 44, ". It is to be appreciated that amplification of a pool of unique differentiator tag sequences may itself introduce bias in the initial pool." Thus the use of unique tags does not inherently correct for bias.

The declaration in section 5 notes the inventor has reviewed the office action. This is noted.

In section 6 the inventor provides his opinion of the distinguishing feature of his invention.

MPEP 716.01(c) states

> Although factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue. While an opinion as to a legal conclusion is not entitled to any weight, the underlying basis for the opinion may be persuasive. *In re Chilowsky,* 306 F.2d 908, 134 USPQ 515 (CCPA 1962) (expert opinion that an application meets the requirements of 35 U.S.C. 112 is not entitled to any weight; however, facts supporting a basis for deciding that the specification complies with 35 U.S.C. 112 are entitled to some weight); *In re Lindell,* 385 F.2d 453, 155 USPQ 521 (CCPA 1967) (Although an affiant's or declarant's opinion on the ultimate legal issue is not evidence in the case, "some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him." 385 F.2d at 456, 155 USPQ at 524 (emphasis in original)).
>
> In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.,* 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied,* 475 U.S. 1017 (1986). See also *In re Oelrich,* 579 F.2d 86, 198 USPQ 210 (CCPA 1978) (factually based expert opinions on the level of ordinary skill in the art were sufficient to rebut the *prima facie* case of obviousness); *Ex parte Gray,* 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989) (statement in publication dismissing the "preliminary identification of a human b-NGF-like molecule" in the prior art, even if considered to be an expert opinion, was inadequate to overcome the rejection based on that prior art because there was no factual evidence supporting the statement); *In re Carroll,* 601 F.2d 1184, 202 USPQ 571 (CCPA 1979) (expert opinion on what the prior art taught, supported by documentary evidence and formulated prior to the making of the claimed invention, received considerable deference); *In re Beattie,* 974 F.2d 1309, 24 USPQ2d 1040 (Fed. Cir. 1992) (declarations of seven persons skilled in the art offering opinion evidence praising the merits of the claimed invention were found to have little value because of a lack of factual support); *Ex parte George*, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991) (conclusory statements that results were "unexpected," unsupported by objective factual evidence, were considered but were not found to be of substantial evidentiary value).

The declaration indicates the claimed method allows for reduction in errors associated with capture and amplification. This argument has been thoroughly

reviewed but is not considered persuasive as the specification teaches on page 44, "It is to be appreciated that amplification of a pool of unique differentiator tag sequences may itself introduce bias in the initial pool." Thus the specification does not suggest the claimed method inherently provides for this outcome, but teaches the unique tags may produce bias.

The response continues by providing the inventors opinion of the teachings of Pourmand and specifically identifies that at one point Pourmand teaches the use of a universal barcode. This argument has been thoroughly reviewed but is not considered persuasive as Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Thus the declaration is picking and choosing teachings of Pourmand to try to overcome the rejection. However, Pourmand has explicitly suggested the use of unique tags.

Further this is a good time to examine the breadth of the claims in view of the teachings of the specification and art. While the claim recites, "a unique differentiator tag," the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, "comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which

hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer." Further the art of Kinciad (USPGPBU 2006/0263789) teaches, " [0008] Methods, systems and computer readable media are provided for sequencing a biopolymer specimen and tracking a source from which the specimen was derived. The biopolymer specimen may be processed to associate a unique identifier therewith, wherein the unique identifier represents metadata identifying a source sample from which the biological specimen was taken." Thus the specification provides no limiting definition of differentiator tag or unique differentiator tag and envisions the differentiator tag can be the target nucleic acid sequence. Thus as Pourmand teaches targeting of specific nucleic acid sequences (which can be considered a unique differentiator tag in view of the specification) and a unique tag in each MIP.

The inventor continues by asserting that Pourmand teaches detection by hybridization. This argument has been thoroughly reviewed but is not considered persuasive as Pourmand also teaches pyrosequencing in step E of figure 1 as reproduced below.

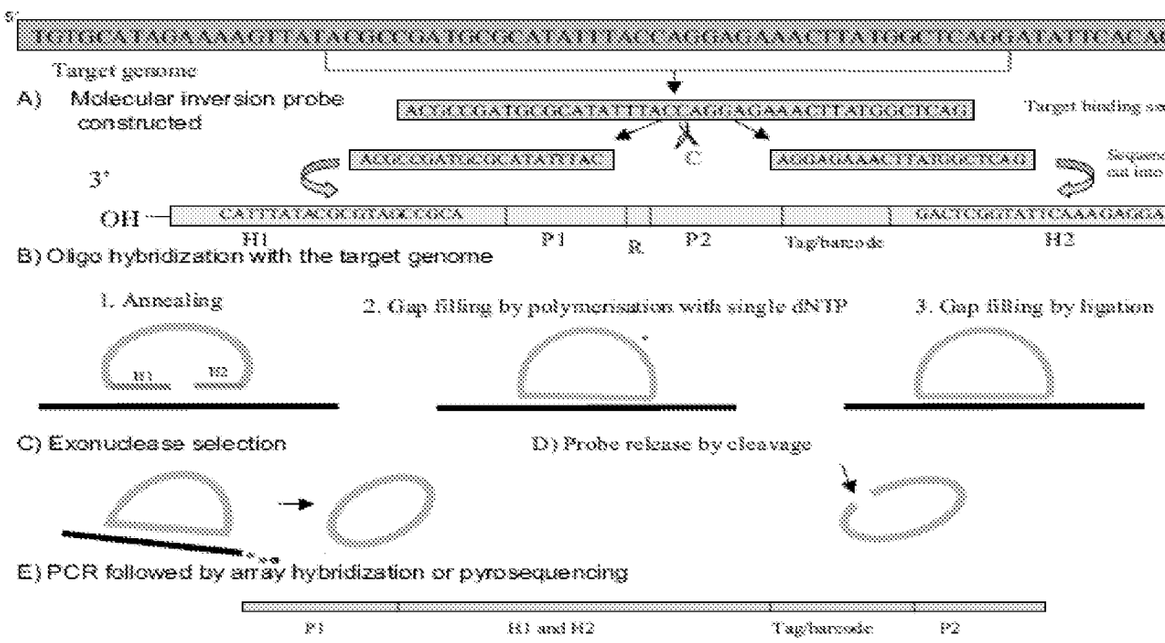

Figure 1

The inventor in section 8 provides his opinion with respect to the microarray detection of Pourmand. This argument is not persuasive as the rejection is drawn to the pyrosequencing taught in figure 1.

The declaration in section 9, provides the inventors opinion with respect to the teachings of Ronaghi. These are noted.

The inventor in section 10 provides his opinion with respect to Ronaghi teaching attaching a unique barcode to each fragment of a BAC library. This assertion appears to be consistent with the inventor's narrow interpretation of the claim.

The inventor continues by asserting the art of Pourmand and Ronaghi do not teach tagging individual with a unique barcode. This argument is not persuasive for the reasons of record as detailed previously.

The response continues by providing argument with respect to Meyer and Shoemaker teach the unique barcoding of each sample. This argument has been thoroughly reviewed but is not considered persuasive as the claims as detailed above encompass unique barcodes for each sample.

Priority

3. The instant application was filed 08/08/2016 is a continuation of 13266862, filed 03/13/2012 and is a national stage entry of PCT/US10/01293 , International Filing Date: 04/30/2010, claims priority from provisional application 61182089, claims priority from provisional application 61179358, filed 05/18/2009, claims priority from provisional application 61178923, filed 05/15/2009, and priority from provisional application 61174470, filed 04/30/2009.

Claim Objections

4. Claim 69 is objected to because of the following informalities:

Claim 69 depends from claim 68 recites, "wherein said identifying step further comprises identifying independent target nucleic acid molecule sequences based on unique differentiator tag[[s]] sequences in each of the sequence reads." Claim 68 recites, "identifying said target nucleic acid molecule sequences based on the differentiator tag sequence of each of the sequence reads.." Thus it is unclear how claim 69 further limits claim 68 as sequencing of the tag appears to identify the target nucleic acids (including independent target nucleic acid molecule sequences) and differentiator tag.

Appropriate correction is required.

Response to Arguments

This is a new ground of objection necessitated by amendment.

Claim Rejections - 35 USC § 102

5. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

6. The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim(s) 68-69, 74-75, 81, is/are rejected under pre-AIA 35 U.S.C. 102 (b) as anticipated by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10)..

While the claim recites, "a unique differentiator tag," the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, "comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer." Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims encompass the same unique tag on every sequence in a sample in view of the amendment.

Further tagging step itself is broad as it provides no limitations with respect to how the tagging is done.

Finally the broadest reasonable interpretation of the identifying step is any analysis that allows for the identification of a target sequence including sequencing data.

With regards to claim 68, Pourmand teaches

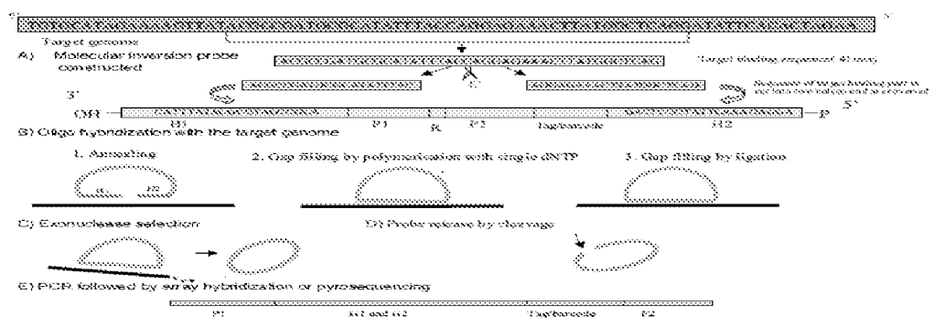

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Pourmand teaches a unique tag as well as target specific sequences which in view of the teachings of the specification are unique differentiator tags.

Pourmand in figure 1 legend specifically teaches pyrosequencing of the MIP probe which encompasses the whole MIP including the target sequence.

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the molecules, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag and the sequence it is attached to..

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Response to Arguments

The response traverses the rejection asserting the 1.132 declaration by the inventor demonstrates the prior art of Pourmand does not teach the unique differentiator tag as required by the claims. This argument has been thoroughly reviewed and is not considered persuasive for the reasons of record, specifically those detailed in response to the declaration and the breadth of the claims.

The response continues by asserting that each individual nucleic acid molecule is tagged with a unique differentiator tag. This argument has been thoroughly reviewed but is not considered persuasive as the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, "comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer." Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims encompass the same unique tag on every sequence on a sample in view of the amendment.

The response continues by relying upon the declaration provided by inventor Porreca. These arguments are not persuasive for the reasons of record.

The response continues by citing the same portion of Pourmand the declaration relies upon with respect to the use of a universal barcode. This argument has been thoroughly reviewed but is not considered persuasive as the teachings of Pourmand is

not limited to the discussion of universal barcodes. Specifically Pourmand at the bottom of the last column of page 2 states, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue I and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and **a unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. The total length of the MIP will be around 100 bases, depending on the lengths of target-binding homologues, primer sequence, restriction site and **unique tag**." Further as detailed in the rejection, the response to the declaration and the instant response to arguments the specification envisions the differentiator tag can be the sequence to which the target nucleic acid hybridizes.

Thus the rejection as modified in view of the amendment is maintained.

8. Claim(s) 68-69, 75, is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Ronaghi (US PGPUB 2006/0008824) .

While the claim recites, "a unique differentiator tag," the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, "comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or

poly-dT reverse-transcription primer." Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims encompass the same unique tag on every sequence on a sample in view of the amendment.

Further tagging step itself is broad as it provides no limitations with respect to how the tagging is done.

Finally the broadest reasonable interpretation of the identifying step is any analysis that allows for the identification of a target sequence including sequencing data.

With regards to claim 68, Ronaghi teaches in claim 10 a method of labeling a nucleic acid by use of a unique primer and amplifying. Ronaghi teaches the amplified sequence can be sequenced (claim 10).

Ronaghi teaches, "the unique primer is attached to the nucleic acid molecule by ligating the adapter comprising a unique barcode to the nucleic acid molecule. In further embodiments, the unique barcode comprises a unique sequence of five nucleotides" (007). Ronaghi teaches each tag is separate sequence from the complementary sequence.

Thus Ronaghi teaches a method of labeling target nucleic acids with a unique primer (or barcode), amplifying and sequencing the amplified sequence, thus identifying the sequence.

Sequencing the amplified sequences encompasses amplifying the unique tag and thus identifying the target sequence.

With regards to claim 69, Ronaghi teaches sequencing the amplified sequence which would identify the unique differentiator tag.

With regards to claim 75, Ronaghi teaches, "In certain embodiments, the source of nucleic acid is selected from the group consisting of: a BAC clone, a bacterium, and a tissue sample.

Response to Arguments

The response asserts Ronaghi teaching attaching a unique barcode to each fragment of a BAC library. This assertion appears to be consistent with the inventor's narrow interpretation of the claim in the declaration. However, the response continues by asserting this is different than what is claimed. However, the claim recites, "tagging each of the plurality of target nucleic acid molecules with a unique differentiator tag thereby generating a plurality of uniquely tagged target nucleic acid molecule." Thus the claims encompass all the target sequences being with the same unique tag.

Thus the rejection is maintained.

Claim Rejections - 35 USC § 103

9. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

10. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the

time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 68-70, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over by Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Meyer (Nature Protocols (2008) volume 3, pages 267-278, epublished Jan 31, 2008).

While the claim recites, "a unique differentiator tag," the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, "comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer." Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims encompass the same unique tag on every sequence on a sample in view of the amendment.

Further tagging step itself is broad as it provides no limitations with respect to how the tagging is done.

Finally the broadest reasonable interpretation of the identifying step is any analysis that allows for the identification of a target sequence including sequencing data.

With regards to claim 68, Pourmand teaches

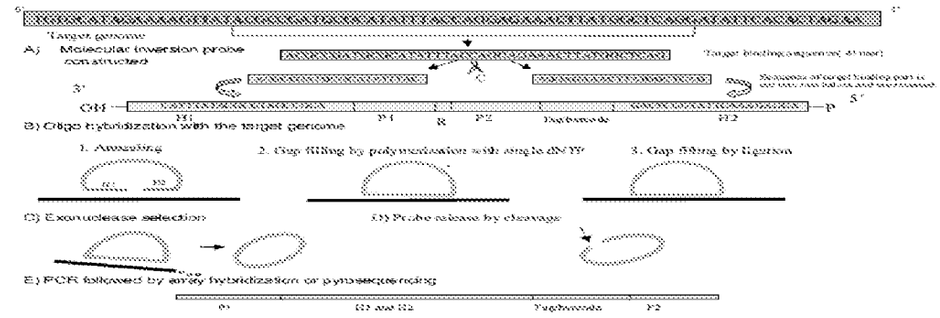

Figure 1

Poumard teaches, “A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Pourmand teaches a unique tag as well as target specific sequences which in view of the teachings of the specification are unique differentiator tags.

Pourmand in figure 1 legend specifically teaches pyrosequencing of the MIP probe which encompasses the whole MIP including the target sequence.

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the molecules, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag and the sequence it is attached to..

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach determining presence of sequencing or amplification errors.

However, Meyer teaches parallel tag sequencing on the massively parallel 454 sequencing platform. Meyers teaches preparing batches of barcoded nucleic acids (unique tags) by attaching barcodes or sequence tags to nucleic acids. Meyers teaches

estimating the false assignment frequency, by identifying the presence of unused tags in sequencing reads (box 1). Meyer further teaches a formula that takes into account and estimates false assignment that occurs due to sequencing errors and cross-contamination of barcoding adapters during synthesis and dilution (Box 1).

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis. .

Response to Arguments

The response traverses by asserting the teachings of the Pourmand does not teach all the limitations of the independent claim. The response further asserts the teachings of Meyers are to a different method of tagging. This argument has been thoroughly reviewed but is not considered persuasive as the rejection is based on the use of tagging to identify sequencing or amplification errors which is obvious over the teachings of Meyer and Pourmand.

12. Claim 68-69, 74-75, 80-82 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Pourmand (BMC informatics (2006) volume 7:500, pages 1-10) and Shoemaker (US20080090239 published 4/17/2008).

While the claim recites, “a unique differentiator tag,” the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, “comprise differentiator tag sequences, and which may be from 15 to 170

nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer." Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims encompass the same unique tag on every sequence on a sample in view of the amendment.

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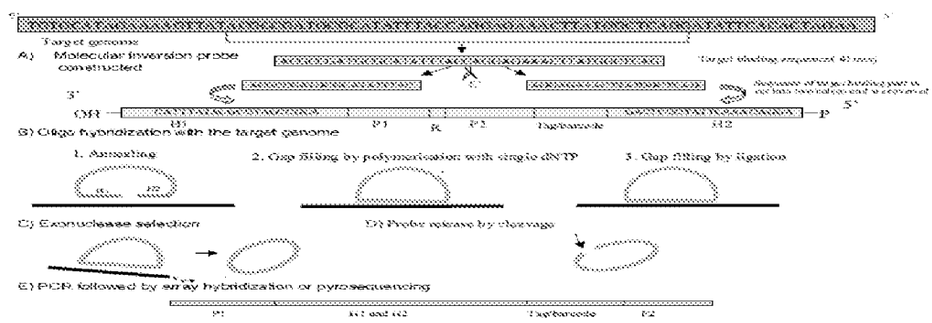

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Pourmand teaches a unique tag as well as target specific sequences which in view of the teachings of the specification are unique differentiator tags.

Pourmand in figure 1 legend specifically teaches pyrosequencing of the MIP probe which encompasses the whole MIP including the target sequence.

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the molecules, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag and the sequence it is attached to..

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Poumard does not specifically teach use of nucleic acids from circulating tumors or fetal nucleic acids.

However, Shoemaker teaches, "[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large number of maternal cells in the blood which make the analysis time consuming and prone to error."

Shoemaker teaches, "0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying, quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc."

Shoemaker teaches, "In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods,

which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detecting circulating tumor nucleic acids or circulating fetal nucleic acids in the method of Poumard. The artisan would be motivated to use methods that are less invasive methods than aminocentesis or tumor biopsy. The artisan would have a reasonable expectation of success as the artisan is merely using known samples in known methods.

Response to Arguments

The response traverses by asserting the teachings of the Pourmand does not teach all the limitations of the independent claim. This argument has been thoroughly reviewed but is not considered persuasive for the reasons of record.

The response continues by arguing the teachings of Shoemaker are to a labeling samples from the cells of origin. This argument has been thoroughly reviewed but is not considered persuasive as the art of Pourmand is being relied upon for the unique tags as detailed in the rejection. The art of Shoemaker is being relied upon solely for the teachings with respect to circulating fetal nucleic acids. Thus the arguments are not consistent with the rejection. The response provides arguments to the use of tags of

Shoemaker not being enabled for the intended purpose. This is not persuasive for the reasons of record.

13. Claim 68-69, 74-75, 80-83 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Ronaghi (US PGPUB 2006/0008824) and Shoemaker (US20080090239 published 4/17/2008).

While the claim recites, "a unique differentiator tag," the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, "comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer." Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims encompass the same unique tag on every sequence on a sample in view of the amendment.

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nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer." Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims encompass the same unique tag on every sequence on a sample in view of the amendment.

Further tagging step itself is broad as it provides no limitations with respect to how the tagging is done.

Finally the broadest reasonable interpretation of the identifying step is any analysis that allows for the identification of a target sequence including sequencing data.

With regards to claim 68, Ronaghi teaches in claim 10 a method of labeling a nucleic acid by use of a unique primer and amplifying. Ronaghi teaches the amplified sequence can be sequenced (claim 10).

Ronaghi teaches, "the unique primer is attached to the nucleic acid molecule by ligating the adapter comprising a unique barcode to the nucleic acid molecule. In further embodiments, the unique barcode comprises a unique sequence of five nucleotides" (007). Ronaghi teaches each tag is separate sequence from the complementary sequence and thus is not locus dependent.

Thus Ronaghi teaches a method of labeling target nucleic acids with a unique primer (or barcode), amplifying and sequencing the amplified sequence, thus identifying the sequence.

Sequencing the amplified sequences encompasses amplifying the unique tag and thus identifying the target sequence.

With regards to claim 69, Ronaghi teaches sequencing the amplified sequence which would identify the unique differentiator tag.

With regards to claim 75, Ronaghi teaches, "In certain embodiments, the source of nucleic acid is selected from the group consisting of: a BAC clone, a bacterium, and a tissue sample.

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which requires, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim 83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags." The broadest reasonable interpretation is the claims require different differentiator tags for different locus, which is anticipated by the claim.

Ronaghi does not specifically teach use of nucleic acids from blood sample, circulating tumors or fetal nucleic acids. Rongahi does not specifically teach determining copy number.

However, Shoemaker teaches, "[0004] The presence of fetal cells within the blood of pregnant women offers the opportunity to develop a prenatal diagnostic that replaces amniocentesis and thereby eliminates the risk of today's invasive diagnostics. However, fetal cells represent a small number of cells against the background of a large

number of maternal cells in the blood which make the analysis time consuming and prone to error."

Shoemaker teaches, "0016] In one embodiment, the invention provides methods for diagnosing a cancer and giving a prognosis by obtaining and enriching a blood sample from a patient for epithelial cells, splitting the enriched sample into discrete locations, and performing one or more molecular and/or morphological analyses on the enriched and split sample. The molecular analyses can include detecting the level of expression or a mutation of gene disclosed in FIG. 10. Preferably, the method comprises performing molecular analyses on EGFR, EpCAM, GA733-2, MUC-1, HER-2, or Claudin-7 in each arrayed cell. The morphological analyses can include identifying, quantifying and/or characterizing mitochondrial DNA, telomerase, or nuclear matrix proteins. In some embodiments, morphological analyses include staining rare cells and imaging the stained rare cells using bright field microscopy, e.g., to determine cell size, cell shape, nuclear size, nuclear shape, the ratio of cytoplasmic to nuclear volume, etc."

Shoemaker teaches, "In some embodiments, the DNA regions can be amplified prior to being quantified. The labeled DNA can be quantified using sequencing methods, which, in some embodiments, can precede amplifying the DNA regions. The amplified DNA region(s) can be analyzed by sequencing methods. For example, ultra deep sequencing can be used to provide an accurate and quantitative measurement of the allele abundances for each STR or SNP. In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes."

Shoemaker teaches, "In other embodiments, quantitative genotyping can be used to declare the presence of fetal cells and to determine the copy numbers of the fetal chromosomes. Preferably, quantitative genotyping is performed using molecular inversion probes" (0010)

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to detecting copy number in circulating tumor nucleic acids or circulating fetal nucleic acids in the method of Ronaghi. The artisan would be motivated to use methods that are less invasive methods than aminocentesis or tumor biopsy to determine copy number.. The artisan would have a reasonable expectation of success as the artisan is merely using known samples in known methods.

Response to Arguments

The arguments with respect to Ronaghi and Shoemaker have been addressed previously and are not persuasive for the reasons of record.

14. Claim 68-70, 74-75, 81 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over by Ronaghi (US PGPUB 2006/0008824) and Meyer (Nature Protocols (2008) volume 3, pages 267-278, epublished Jan 31, 2008).

While the claim recites, "a unique differentiator tag," the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, "comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it." Further page 44 of the specification recites, "Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or

poly-dT reverse-transcription primer." Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims encompass the same unique tag on every sequence on a sample in view of the amendment.

Further tagging step itself is broad as it provides no limitations with respect to how the tagging is done.

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With regards to claim 68, Ronaghi teaches in claim 10 a method of labeling a nucleic acid by use of a unique primer and amplifying. Ronaghi teaches the amplified sequence can be sequenced (claim 10).

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With regards to claim 69, Ronaghi teaches sequencing the amplified sequence which would identify the unique differentiator tag.

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Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which requires, "tagging each target nucleic acid molecule from the biological sample with one or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim 83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags." The broadest reasonable interpretation is the claims require different differentiator tags for different locus, which is anticipated by the claim.

Ronaghi does not specifically teach determining presence of sequencing or amplification errors.

However, Meyer teaches preparing batches of barcoded nucleic acids (unique tags) by attaching barcodes or sequence tags to nucleic acids. See p. 271, Box 1; Quality control and Procedure. The barcodes are added to purified PCR products or positive control PCR products (p. 272, Reagent Setup; p. 273, step 10). The batches are pooled and sequenced in parallel. A contamination in a batch of barcodes is determined by determining a frequency at which cross-contamination of adapters occurred during synthesis or dilution. Meyer further teaches a formula that takes into

account and estimates false assignment that occurs due to sequencing errors and cross-contamination of barcoding adapters during synthesis and dilution (Box 1). Therefore, Meyer teaches identifying a contamination in a batch of barcodes (unique tags)by determining a frequency at which an incorrect adapter sequence occurs in the batches.

Therefore it would have been prima facie obvious to one of ordinary skill in the art to examine sequencing or amplification errors. The artisan would be motivated to examiner sequencing and tagging errors as the art recognizes these errors happen in tagging and sequencing of sequences. The artisan would have a reasonable expectation of success as the artisan is merely applying known methods of error detection to known methods of sequence analysis. .

Response to Arguments

The arguments with respect to Ronaghi and Meyer have been addressed previously and are not persuasive for the reasons of record.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46

USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

16. Claims 68-70, 74-75, 80-82 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 13/266,862 in view of Pourmand (BMC informatics (2006) volume 7:500, pages 1-10). This is a provisional nonstatutory double patenting rejection.

The instant claims are drawn to a method for nucleic acid identification, the method comprising the steps of: obtaining a biological sample comprising a plurality of target nucleic acid molecules; tagging each of the plurality of target nucleic acid molecules with a unique differentiator tag, thereby generating a plurality of uniquely tagged target nucleic acid molecule; amplifying each of the plurality of ~~said~~ uniquely tagged target nucleic acid molecules to generate amplicons of each ~~that contain the~~ uniquely tagged target nucleic acid molecule; sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence; and identifying said target nucleic acid molecule sequences based on the differentiator tag sequence of each of the sequence reads.

While the claim recites, “a unique differentiator tag,” the specification does not teach a limiting definition of such tag, but provides numerous examples including page 7 which states, “comprise differentiator tag sequences, and which may be from 15 to 170 nucleotides in length, are used which hybridize along the length of a target region of a genetic locus to immobilize it.” Further page 44 of the specification recites, “Another method to incorporate the differentiator tag sequences is as a tag on a gene-specific or poly-dT reverse-transcription primer.” Thus a unique differentiator tag is broad and encompasses sequences which hybridize to target sequences. Further the claims

encompass the same unique tag on every sequence on a sample in view of the amendment.

Further tagging step itself is broad as it provides no limitations with respect to how the tagging is done.

Finally the broadest reasonable interpretation of the identifying step is any analysis that allows for the identification of a target sequence including sequencing data.

Claim 1 of '862 is drawn to A method for analyzing a target nucleic acid, the method comprising: providing a sample comprising a target nucleic acid, contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes (MIPs), each MIP comprising a 5' targeting arm, a central region, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the target nucleic acid, wherein the probe set has a staggered layout such that all of the MIPs capture the target, and some MIPs in the probe set capture additional flanking sequence; converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target nucleic acid; isolating the plurality of circularized probes; and acid sequences of different subregions; and analyzing the isolated subregions.

Claims of '862 do not specifically teach amplifying or a unique barcode.

Claim 68 has been amended to recite, ""locus independent differentiator tags." Locus independent differentiator tags" is not an art accepted term. The specification does not recite, "locus independent differentiator tags." Thus the specification does not provide any definition or standard by which to determine what is required of a "locus

independent differentiator tags." Thus the broadest reasonable interpretation of "locus independent differentiator tags" is a tag that does not comprise nucleotides of the locus.

With regards to claim 68, Pourmand teaches

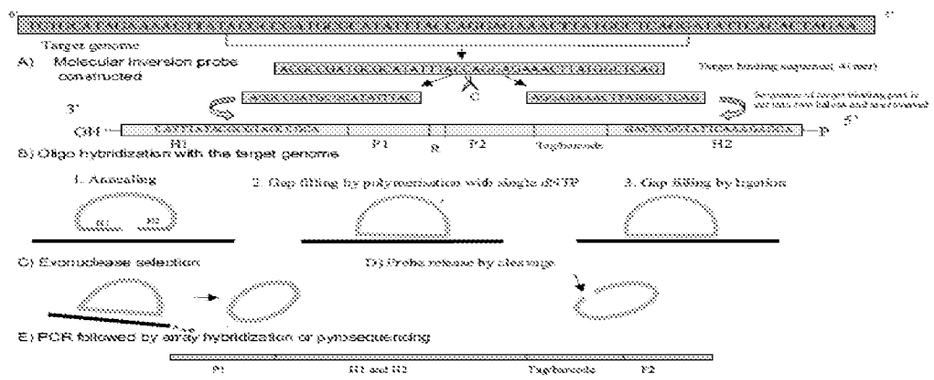

Figure 1

Poumard teaches, "A molecular inversion probe (Figure 1A) consists of two target specific binding segments, called homologue1 and homologue2, that are homologous to the target sequence and are separated by an optional single common middle base nucleotide (A, G, T, or C) in the target. In a MIP, these homologues are separated by two or more tag sequences, which include a universal primer pair for the amplification of all the target bound probes, and a **unique tag** which detects and identifies each of the probes after binding to the target specifically. The MIP also may contain an optional restriction or cleavage site. (page 2, 2nd column). Pourmand teaches each tag is separate from the target specific sequences and thus is not locus dependent.

Thus Poumard teaches a method of applying a unique tag to each of a plurality of nucleic acids, amplifying the molecules, sequencing and identifying the sequence by the sequencing.

With regards to claim 69. Poumard teaches sequencing which identifies the unique tag.

With regards to claim 74-75, Poumard teaches, "We used the PathogenMIPer software to design MIPs for 105 different types of human papilloma viruses (HPV). These genomes differ only slightly at most of the regions. Input constraints included a Tm of 60°C, length of 50 bp and middle base G. Multiple probes were designed for each target pathogen, and these probes complement different regions of the genome in order to exploit the variability of the whole genome and detect even small copies of the pathogen in the sample. In a preliminary test, twenty-four of the resulting probes (see Table 1) were used in a MIP assay designed for very sensitive detection of multiple pathogens in a sample. These 24 probes were selected in such a way, representing the 24 most common HPV genotypes, associated with human infections ranging from genital and oral warts to cervical, and oral carcinomas, as reported in several clinical studies. The clinical samples, containing extracted total genomic DNA from cervical tumor scrapes, were obtained from Oncomatrix [25].(2nd column page 4 to 1st column page 5).

With regards to claim 81, Poumard teaches, "MIP assays are promising for a number of clinical diagnostic applications such as detection of microbial co-infections, antibiotic resistance and measurements of microbial copy number in a single tube."(page 2, column 1, 1st full paragraph).

Claim 83 has been added by amendment and recites, "wherein a same set of differentiator tags is used across multiple loci." Claim 83 depends from claim 68 which requires, "tagging each target nucleic acid molecule from the biological sample with one

or more of a plurality of random locus-independent differentiator tags, thereby generating a plurality of tagged target nucleic acid molecules." Thus dependent claim 83 appears to require the use of the same differentiator tags in multiple loci, which appears to contradict the use of "random locus-independent differentiator tags." The broadest reasonable interpretation is the claims require different differentiator tags for different locus, which is anticipated by the claim.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to improve the molecular inversion probe method of '862 with unique differentiator tags with amplifying and sequencing of Poumard. The artisan would be motivated to amplify and sequence the molecular inversion probes to increase the amount of nucleic acid being detected and thus increase the sensitivity by an art . The artisan would have a reasonable expectation of success as the artisan is merely be using art accepted methods of analysis of nucleic acid sequences using molecular inversion probes.

Response to Arguments

The response request the ODP rejection be held in abeyance. Thus the rejection is maintained.

Summary

No claims are allowed.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C POHNERT PhD whose telephone number is

(571)272-3803. The examiner can normally be reached on Monday- Friday about 6:00 AM-5:30 PM, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Steven Pohnert/
Primary Examiner, Art Unit 1634

Notice of References Cited	Application/Control No. 15/231,687	Applicant(s)/Patent Under Reexamination Porreca et al.	
	Examiner STEVEN C POHNERT PhD	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20060263789-A1	11-2006	Kincaid; Robert	C12Q1/68	435/6.12
	B					
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/04US 34468/10

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2020-06-26
Name/Print	Thomas C. Meyers	Registration Number	36,989

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4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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(Not for submission under 37 CFR 1.99)

Application Number	15231687
Filing Date	2016-08-08
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	MLB-002/04US 34468/10

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	Application Number	15231687
	Filing Date	2016-08-08
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/04US 34468/10

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/SP/	1	Abravaya, 1995, Detection of point mutations with a modified ligase chain reaction (Gap-LCR), Nucleic Acids Research, 23(4): 675-682	
/SP/	2	Bhangale, 2006, Automating resequencing-based detection of insertion-deletion polymorphisms, Nature Genetics 38:1457-1462	
/SP/	3	Final Rejection issued in U.S. Application No. 13/266,862, date of mailing: June 9, 2020, 33 pages	
/SP/	4	Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign_sd&utm_medium=serp&utm_source=jsonld), downloaded June 3, 2020, 9 pages	

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Examiner Signature	/Steven Pohnert/ (07/08/2020)	Date Considered	07/08/2020

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Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Sandra Richards
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	02-OCT-2020
Filing Date:	08-AUG-2016
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Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		MLB-002-04US-RESPONSE.pdf	45573 10789f30d61ec0af1e3a901b3dfbd34bed87f44f	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	11
Warnings:			
Information:			
	Total Files Size (in bytes):	45573	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

This paper is in response to a non-final Office Action mailed July 14, 2020 from the United States Patent and Trademark Office.

Amendments to the claims begin on page 2.

Remarks begin on page 6.

Applicant believes no fees are due with this paper. Nevertheless, Applicant authorizes any required fees due with this response to be charged to Deposit Account No. 50-0369.

AMENDMENTS TO THE CLAIMS

Please amend the claims as follows. The following listing of claims will replace all prior versions of claims in the application.

1-67. (Canceled)

68. (Currently Amended) A method for correcting for errors or bias introduced during nucleic acid analysis workflow~~identification~~, the method comprising the steps of:

obtaining a biological sample comprising a plurality of target nucleic acid molecules from more than one locus of origin;

introducing a set of differentiator tags, wherein members of said set of differentiator tags are associated with members of said plurality, such that one or more of said loci of origin are associated with more than one differentiator tag;

~~tagging each of the plurality of target nucleic acid molecules with a unique differentiator tag, thereby generating a plurality of uniquely tagged target nucleic acid molecule~~;

amplifying each of the plurality of ~~uniquely~~ tagged target nucleic acid molecules to generate ampliconsof each uniquely tagged target nucleic acid molecule;

sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence; and

correcting for error or bias introduced during said workflow by collapsing target:differentiator tag combinations observed more than once into a single count; ~~and~~

~~identifying said target nucleic acid molecule sequences based on the differentiator tag sequence of each of the sequence reads~~.

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69. (Currently Amended) The method of claim 68, wherein said ~~identifying~~ correcting step further comprises collapsing all sequence reads comprising a same differentiator tag into a single read before determining a consensus base call for the ~~identifying independent~~ target nucleic acid molecule sequences ~~based on unique differentiator tag sequences in each of the sequence reads~~.

70. (Previously Presented) The method of claim 69, further comprising the step of determining the presence of a sequencing or amplification error based upon a number of said ~~unique~~ differentiator tag sequences.

71. (Withdrawn) The method of claim 68, further comprising the step of applying a common identifier tag to members of said plurality of nucleic acid molecules.

72. (Withdrawn) The method of claim 71, wherein said common identifier is used to identify a sample source.

73. (Withdrawn) The method of claim 72, wherein said common identifier is used to identify a patient.

74. (Previously Presented) The method of claim 68, wherein said biological sample is selected from the group consisting of blood and biopsy tissue.

75. (Previously Presented) The method of claim 68, wherein said plurality of target nucleic acid molecules comprises bacterial or viral nucleic acids isolated from said biological sample.

76. (Withdrawn) The method of claim 68, further comprising the step of genotyping a patient from whom said biological sample is obtained.

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77. (Withdrawn) The method of claim 76, further comprising the step of diagnosing a condition based upon said genotyping.

78. (Withdrawn) The method of claim 68, further comprising the step of determining the copy number of a genomic region in a patient from whom said biological sample is obtained.

79. (Canceled)

80. (Previously Presented) The method of claim 68, wherein said plurality of target nucleic acid molecules are circulating tumor nucleic acid molecules.

81. (Previously Presented) The method of claim 68, further comprising the step of determining the copy number of a genomic region or transcript in a patient from whom the sample is obtained.

82. (Previously Presented) The method of claim 68, wherein said plurality of target nucleic acid molecules are maternally-circulating fetal or placental nucleic acid molecules.

83. (Canceled)

84. (New) A method for correcting for errors or bias introduced during nucleic acid analysis workflow, the method comprising the steps of:

obtaining a biological sample comprising a plurality of target nucleic acid molecules from more than one locus of origin;

introducing a set of unique differentiator tags, wherein members of said set of differentiator tags are randomly associated with members of said plurality, such that any given tag is uniquely associated with said locus of origin;

amplifying each of the plurality of tagged target nucleic acid molecules to generate amplicons;

sequencing the amplicons obtained in said amplifying step to obtain sequence reads of each of the amplicons, wherein each of the sequence reads comprises a target nucleic acid molecule sequence and a differentiator tag sequence; and

correcting for error or bias introduced during said workflow by recognizing target/differentiator tags having the same sequence as being derived from the same input molecule.

Remarks

Claims 68-78 and 80-82 and 84 are pending in the application. Claims 68 and 69 are amended and claim 84 is added. Support for the claim amendments is found throughout the as-filed application, for example at page 6 (lines 21-24), page 39 (lines 21-26), page 40 (lines 7-9), page 41 (lines 3-22) and page 42 (lines 13-27). No new matter is added.

Claim Objections

Claim 69 is objected to as failing to further limit claim 68 upon which it depends. Amended claim 69 contains an additional element of collapsing sequencing reads comprising the same differentiator tag to determine consensus base calls for the target nucleic acid molecule sequences. Applicant respectfully submits that such an element is not found in claim 68 and, therefore, believes that the objections are overcome.

Prior Art Rejections

Claims 68-69, 74-75, 81, and 83 are rejected under 35 U.S.C. §102(b) over Pourmand, et al. (BMC Informatics (2006) volume 7:500, pages 1-10). The Office Action, at page 11, states that claims 68-69, 75, and 83 are rejected under 35 U.S.C. §102(b) over US PGPUB 2006/0008824 of Ronaghi. The Office Action, at page 14, states claims 68-70, 74-75, and 81 are rejected under 35 U.S.C. §103(a) over Pourmand and Meyer, et al. (Nature Protocols (2008) volume 3, pages 267-278, epublished January 31, 2008); at page 22, that claims 68-69, 74-75, and 80-83 over Ronaghi and US20080090239 of Shoemaker; and at page 26, that claims 68-70, 74-75, and 81 over Ronaghi and Meyer.

In order to anticipate a claim, the Patent Office requires that a reference show each and every element of the claim. MPEP §2131. In order to establish a *prima facie* case of obviousness, there must be a suggestion in the cited art to modify a reference or to combine multiple

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references in a manner that would lead one of ordinary skill in the art to an applicant's claimed invention. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Office Action states at numerous points that the term "differentiator tag" is not given a specific limiting definition in the specification and that the claims encompass the same unique tag on every sequence on a sample. (See page 3 of the Office Action stating that the argument put forth in the declaration is not persuasive because it "…is attempting to assert each nucleic has its own unique tag. However the claim requires tagging a plurality of target nucleic acid molecules with a unique tag, which encompasses a single unique tag which is same but unique on all target molecules.").

In response, Applicant has clarified the claims to make clear that target nucleic acids (loci) may be associated with more than one tag. Thus, a given locus may be associated with more than one unique identifier tag. However, in the "correcting" step, target:differentiator tag combinations that are observed more than once are collapsed into a single count. Doing so will, for example, correct for PCR bias or errors introduced during the amplifying step. However, there can be other copies of the same locus that are associated with a different differentiator tag and, while those are collapsed together to the extent there are multiple copies of them, they are never collapsed with other target:differentiator tag combinations. Example 3 in the as-filed application explains further as exemplified beginning at line 21 of page 39 of the as-filed specification as follows:

> Aspects of the invention relate to associating unique sequence tags (referred to as differentiator tag sequences) with individual target molecules that are independently captured and/or analyzed (e.g., prior to amplification or other process that may introduce bias). These tags are useful to distinguish independent target molecules from each other thereby allowing an analysis to be based on a known number of individual target molecules. For example, if each of a plurality of target molecule sequences obtained in an assay is associated with a different differentiator tag, then the target sequences can be considered to be independent of each other and a genotype likelihood can be determined based on this information. In contrast, if each of the plurality of target molecule sequences

> obtained in the assay is associated with the same differentiator tag, then they probably all originated from the same target molecule due to over-representation (e.g., due to biased amplification) of this target molecule in the assay.

By randomly tagging starting target molecules, subsequent amplification or sequencing bias and/or error is eliminated by collapsing any target:differentiator tag combination observed more than once into a single read before consensus base calls are determined. See Amended Claim 69 and Example 2 of the as-filed specification. As noted above, sequences associated with the same differentiator tag originated from the same target molecule due to over-representation and, accordingly, collapsing those sequences before consensus base calling allows each original molecule sequence to only be counted once and eliminates outsized influence on consensus base calls caused by bias or error introduced during the amplification and sequencing processes. Applicant believes that the claims are unambiguous in the scope and purpose of the unique differentiator tags.

Applicant objects to the summary dismissal of Dr. Porreca's declaration under 37 C.F.R. 1.132 and Applicant requests that the Examiner consider Dr. Porreca's conclusions or provide evidence or a counter-declaration refuting those conclusions. Dr. Porreca is a recognized expert in the field and his opinion carries significant weight with respect to the matters on which he is an expert. It is inappropriate for the Examiner to maintain a rejection based upon conclusory statements and, further, the Examiner has provided no evidence or reasoning to give basis for conclusion that his technical views take precedence over those of an expert in the field. *See, e.g., In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); *see also KSR Int'l Co. v. Teleflex Inc*, 550 U.S. 398, 418, 82 USPQ2d at 1396; MPEP §2145. The fact that an affiant is the inventor of the technology is not, alone, a basis for dismissal of the expert's opinions on technical matters. *Ex parte Keyes,* 214 USPQ 579 (Bd. App. 1982); *In re McKenna,* 203 F.2d 717, 97 USPQ 348 (CCPA 1953). In this case, it is only because Dr. Porreca is the recognized expert in the field that he was able to arrive at the insights that led to the claimed invention. Dr. Porreca provides his expert analysis on the distinctions between his invention and the cited art.

Moreover, Dr. Porreca has not based his conclusions on legal analysis. Applicant respectfully urges the Examiner to give Dr. Porreca's declaration due consideration or to provide evidence that Dr. Porreca's technical conclusions are wrong. If the Examiner believes that he is an expert in the field, Applicant respectfully requests that the Examiner submit his own affidavit attesting to such expertise. Failing that, Applicant urges the Examiner to accept the technical conclusions of the expert affidavit submitted by the Applicant.

Also, in view of the clarifying amendments, Applicant maintains and resubmits the arguments previously made against anticipation and obviousness. Specifically, none of the cited references teach or suggest tagging the same locus (multiple copies) with more than one differentiator tag.

A difference between the present claims and the cited prior art is the idea that multiple copies of a locus may be associated with different tags, but that in order to correct for error or bias and copies of a locus having the same tag must be collapsed into a single count. As discussed in prior responses and reiterated below, no combination of the cited references teaches or suggests those claimed features.

Pourmand reports a universal barcode sequence that allows for array detection and quantification of the amplified probe. *Pourmand*, pg. 2, col. 1, par. 3. (emphasis added). Pourmand reports using its universal barcode sequence for pathogen identification and detection. *Id.,* abstract. Accordingly, Pourmand relies on at least thousands of copies of the **same** barcode hybridized to the same target molecule to genotype and thus detect pathogens by microarray. In no way then can Pourmand suggest the claimed method which essentially allows random assignment of tags to loci. Moreover, Pourmand does not disclose or suggest the step of collapsing same locus:tag combinations into a single count.

Ronaghi reports using a barcode unique to a specific BAC library to distinguish which BAC library clonal amplification products are cloned from in order to ensure sequence assembly of clonal amplification products derived from the same source BAC library. *Ronaghi*, (lines 14-

26) of [0015]; [0058]. The "unique" barcodes reported in Ronaghi are unique only to all of the fragments coming from a BAC library for source library identification. Thus, in contrast to the present invention, Ronaghi reports batch tagging wherein more than one originating nucleic acid molecule shares the same tag. Ronaghi's methods of batch tagging are well suited to identifying a library but one of skill in the art would have found no suggestion to modify the tags to be unique to each molecule as doing so would frustrate the sample or batch tagging purpose of Ronaghi.

Applicant maintains that the secondary references of Meyer and Shoemaker do not make up for what Pourmand and Ronaghi lack.

Meyer reports achieving parallel tagged sequencing by barcoding each sample with a specific tag sequence. *Meyer,* pg. 267, col. 2, par. 2. Shoemaker reports using unique labels to identify which cell DNA originates from in a mixed sample. *Shoemaker*, (lines 5-6) of [0009]. Both samples apply the same tag to multiple originating nucleic acids in order to trace back multiplex sequencing results to a sample or source cell but NOT to a specific originating nucleic acid as in the present claims.

Because an element of the claims (each target nucleic acid having its own unique tag) is completely absent from the cited references, Applicant believes that the prior art rejections have been overcome and their withdrawal is accordingly requested.

Double Patenting

Claims 68-70, 74, 75, and 79-82 are provisionally rejected on the ground of nonstatutory double patenting over claim 1 of co-pending Application No. 13/266,862 in view of Pourmand.

Applicant believes submission of a Terminal Disclaimer for the above referenced application at this time would be premature. Applicant will address the above referenced application the application is deemed allowable. Applicant believes the double patenting rejection is addressed.

Summary

Applicant respectfully submits that the presently amended claims are in condition for allowance, which is respectfully requested. If there are any questions regarding the above remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: October 2, 2020

Respectfully submitted,
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Petitioner Illumina, Inc., EX1003, p. 1267

UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Nov 3 2020

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Daniel A Palmer

S-signature:
/Daniel A Palmer/

Registration Number:
73994

U.S. Application Number:
15231687

Confirmation Number:
6709

E-mail Address:
dpalmer@brownrudnick.com

Phone Number:
+1 6178347501

Proposed Time of Interview:
11-10-2020 1:00 PM ET

Prefered Interview Type:
Telephonic

I am the applicant or applicant's representative for this application.

Topic for Discussion:

uspto UNITED STATES PATENT AND TRADEMARK OFFICE

Electronic Acknowledgement Receipt	
EFS ID:	41162193
Application Number:	15231687
International Application Number:	
Confirmation Number:	6709
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Casey Suda
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/04US 34468/10
Receipt Date:	18-NOV-2020
Filing Date:	08-AUG-2016
Time Stamp:	18:41:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$320
RAM confirmation Number	E2020AHI42360236
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Req. Reconsideration-After Non-Final Reject	MLB-002-04US-EOT-Transmittal.pdf	75847 b7f9ca8b83d55a5bda2b6bf052fcd7b9b217e415	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30859 2f0cb5793f607fddc2650d28f6538e54f3521c28	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	106706		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket No.: MLB-002/04US 34468/10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
SERIAL NUMBER:	15/231,687	CONF. NO.:	6709
FILING DATE:	August 8, 2016	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

FILED ELECTRONICALLY

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

RESPONSE AND AMENDMENT

This paper is in response to the non-final Office Action mailed July 14, 2020 from the United States Patent and Trademark Office. Applicant believes that the amendment and response filed on October 2, 2020 was responsive that co-pendency is therefore established with a continuation application being filed today. However, in order to ensure co-pendency, Applicant petitions for and requests a 2-month extension of time and submits herewith the associated EOT fee. Applicants authorize the Commissioner to charge any other required fees to Deposit Account No. 500369.

Dated: November 18, 2020

Respectfully submitted,
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63910843 v1

Electronic Patent Application Fee Transmittal

Application Number:	15231687
Filing Date:	08-Aug-2016
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Casey Suda
Attorney Docket Number:	MLB-002/04US 34468/10

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	2252	1	320	320
Miscellaneous:				
		Total in USD ($)		**320**

Applicant-Initiated Interview Summary	**Application No.** 15/231,687	**Applicant(s)** Porreca et al.	
	Examiner STEVEN C POHNERT PhD	**Art Unit** 1634	**AIA (FITF) Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) STEVEN C. POHNERT PhD.

(3) Greg Poreca.

(2) Thomas Meyers.

(4) _____.

Date of Interview: 18 November 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☑Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 68 and 84.

Identification of prior art discussed: cite.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The representative noted the amendments to clarify the invention. The examiner noted that the amendments provide a new invention drawn to correcting errors or bias. The examiner indicated that it was improper to switch inventions, to which the representative asserted the intent of the application from the beginning was to allow for correction of errors or bias. The examiner noted the originally filed claims did not provide for such limitations and thus the instant claims were a distinct invention. The examiner agreed with the representative that if applicant and inventor wanted the instant claims to be examined the best course would be to file a continuation. The examiner noted applicant could also delete the limitations with respect to correcting errors and bias and revert to claims for nucleic acid identification to allow the originally presented invention to be examined. No agreement on patentability was reached..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

	/Steven Pohnert/ Primary Examiner, Art Unit 1634

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 11/23/2020

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/23/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
15/231,687	08/08/2016	Porreca et al.	MLB-002/04US 3446

	EXAMINER	
BROWN RUDNICK LLP ONE FINANCIAL CENTER BOSTON, MA 02111	STEVEN C POHNERT PhD	
	ART UNIT	PAPER
	1634	20201118

DATE MAILED: _____

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

The amendment filed on 10/2/20 has amended all claims drawn to the elected invention and presenting only claims drawn to a new invention is non-responsive (MPEP § 821.03) and has not been entered. The remaining claims are not readable on a new elected invention because Newly submitted claim 84 and amended claim 68 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Methods of correcting errors or bias introduced during nucleic acid analysis workflow has a different effect and outcome and is not an obvious variant of method of nucleic acid identification. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Since the above-mentioned amendment appears to be a bona fide attempt to reply, applicant is given a shortened statutory period of TWO (2) MONTHS from the mailing date of this notice within which to supply the omission or correction in order to avoid abandonment. EXTENSIONS OF THIS TIME PERIOD UNDER 37 CFR 1.136(a) ARE AVAILABLE but in no case can any extension carry the date for reply to this letter beyond the maximum period of SIX MONTHS set by statute (35 U.S.C. 133).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C POHNERT PhD whose telephone number is (571)272-3803. The examiner can normally be reached on Monday- Friday about 6:00 AM-5:30 PM, every second Friday off.

	/Steven Pohnert/ Primary Examiner, Art Unit 1634

PTO-90C (Rev.04-03)

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/231,687	08/08/2016	Gregory Porreca	MLB-002/04US 34468/10	6709

21710 7590 07/28/2021

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
07/28/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@brownrudnick.com
usactions@brownrudnick.com

Notice of Abandonment	Application No.	Applicant(s)
	15/231,687	Porreca et al.
	Examiner	Art Unit
	STEVEN C POHNERT PhD	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☑ Applicant's failure to timely file a proper reply to the Office letter mailed on 23 November 2020.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 to the final rejection. (A proper reply under 37 CFR 1.113 to a final rejection consists only of:(1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) if this is utility or plant application, a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. Note that RCEs are not permitted in design applications.)
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a *bona fide* attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 8 below).
   (d) ☑ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $ _____ is insufficient. A balance of $ _____ is due.
   The issue fee required by 37CFR 1.18 is $ _____ . The publication fee, if required by 37 CFR 1.18(d), is $ _____ .
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record or other party authorized under 37 CFR 1.33 (b). See 37 CFR 1.138(b).

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34) upon the filing of a continuing application.

6. ☐ The decision by the Patent Trial and Appeal Board rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The dismissal of the appeal in an application having no allowed claims. (When an appeal is dismissed in an application having no allowed claims the application stands abandoned. See MPEP 1215.04 subsections I-V for an explanation of the reasons why an appeal is dismissed.)

8. ☐ The reason(s) below:

_____

/Steven Pohnert/ Primary Examiner, Art Unit 1634	

Petitions to revive under 37 CFR 1.137, or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

Petitioner Illumina, Inc., EX1003, p. 1279

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/231,687

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	11 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	730		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/231,687

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	11 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	730		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/231,687

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	11 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	730		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/08/2016	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 11	Minus	** 20	=	X $ =	
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
TERRANCE LAWRENCE

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	03/31/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 15	Minus	** 20	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
VENESSA JONES

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT

09/06/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
BRENDA HARRISON

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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/27/2018	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
LINDA HUMES

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	12/05/2018							
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT								
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARSHA R RICHARDS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/28/2018	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $50 =	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $230 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

SLIE
DEIDRE C. KING-WOODWARD

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	10/24/2019							
	Total (37 CFR 1.16(i))	* 15	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT								
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CHRISTINE V MOORE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT	02/18/2020	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARSHA R RICHARDS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	03/12/2020							
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $230 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT								
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MOLIKI I MAY/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/231,687	Filing Date 08/08/2016	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $210 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	10/02/2020							
	Total (37 CFR 1.16(i))	* 15	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT								
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CHRISTINE V MOORE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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