Notice of References Cited	Application/Control No. 13/266,862	Applicant(s)/Patent Under Reexamination PORRECA ET AL.	
	Examiner STEVEN POHNERT	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-				
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FOREIGN PATENT DOCUMENTS

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	N					
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	P					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Ericsson et al (Nucleic Acids Research 2008) volume 36, e45, published on March 16, 2008)
	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., EX1002, p. 1092

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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)	2015-09-24
Name/Print	Thomas C. Meyers	Registration Number	36989

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

PTO/SB/08a (03-15)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13266862
Filing Date	2012-03-13
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	GSGE-002/01US 29258/20

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
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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]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

/S.P./	1	Diep et al., 2012, Library-free methylation sequencing with bisulfite padlock probes, Nature Methods 9:270-272 (and supplemental information)	☐
/S.P./	2	Flaschker et al., 2007, Description of the mutations in 15 subjects with variant forms of maple syrup urine disease, J Inherit Metab Dis 30:903-909	☐
/S.P./	3	Saihan et all., 2009, Update on Usher syndrome, Current Opinion in Neurology 22:19-27	☐

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EXAMINER SIGNATURE

Examiner Signature	/Steven Pohnert/ (01/12/2016)	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.

Electronic Acknowledgement Receipt

EFS ID:	25555074
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Lauren Poon
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/01US 29258/20
Receipt Date:	21-APR-2016
Filing Date:	13-MAR-2012
Time Stamp:	12:10:30
Application Type:	U.S. National Stage under 35 USC 371

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		GSGE-002-01US-Response-to-NFOA-012216.pdf	44045 192ff0e83d310be65db8265ed71ad6d1582 45cc2	yes	13

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	8
	Applicant Arguments/Remarks Made in an Amendment	9	13
Warnings:			
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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.

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	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 the non-final office action mailed January 22, 2016, from the United States Patent and Trademark Office. Applicants believe no fee is due. Nevertheless, Applicants authorize the Commissioner to charge any required fee to Deposit Account No. 500369.

Amendments to the claims begin on page 2.

Remarks begin on page 9.

Amendment to the claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Previously Presented) 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; and

a central region flanked by the 5' region and the 3' region;

wherein the 5' region and 3' region of each probe are complementary to nucleic acid residues flanking the same strand of one of a plurality of subregions of the target nucleic acid;

wherein each subregion is different and overlaps with at least one other subregion;

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; and

wherein at least two of the plurality of molecular inversion probes are present at different concentrations in the probe set;

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.

2. (Previously Presented) The method of claim 1, wherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence.

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3. (Original) 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. (Original) 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.

5-11. (Canceled)

12. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 12, 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. (Withdrawn) The method of claim 12, wherein the threshold number for a specific target nucleic acid sequence is selected based on a desired statistical confidence for the genotype.

16. (Withdrawn) The method of claim 12, further comprising determining a statistical confidence for the genotype based on the number of unique combinations of target nucleic acid and differentiator tag sequences.

17-19. (Canceled)

20. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 20, wherein the capture efficiency is lower than the reference capture efficiency.

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

24. (Withdrawn) The method of claim 20, wherein the capture efficiency is higher than the reference capture efficiency.

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

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

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

28. (Withdrawn) The method of claim 20, wherein a sub-target nucleic acid is captured from the target nucleic acid using a molecular inversion probe.

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

31-32. (Canceled)

33. (Withdrawn) The method of claim 29, wherein the first and second targeting arms have the same length.

34-35. (Canceled)

36. (Withdrawn) The method of claim 29, wherein the hybridization Tms of the first and second targeting arms are identical.

37. (Withdrawn) The method of claim 28, wherein the sub-target nucleic acid contains a nucleic acid repeat.

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

39. (Canceled)

40. (Withdrawn) 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. (Withdrawn) The method of claim 29, 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.

42. (Withdrawn) The method of claim 29, 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.

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43. (Withdrawn) The method of claim 29, 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. (Withdrawn) The method of claim 20, wherein a plurality of different target nucleic acids are analyzed in a biological sample.

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

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

48-49. (Canceled)

50. (Withdrawn) The method of claim 20, wherein the capture efficiency is evaluated by determining an amount of target nucleic acid that is captured.

51. (Withdrawn) 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.

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

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53. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 20, 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.

57-67. (Canceled)

Petitioner Illumina, Inc., EX1002, p. 1106

Remarks

Claims 1-4 are pending in the application. No claims are amended and no new matter is added.

Rejection under 35 U.S.C. §112, first paragraph

The Office Action rejects claims 1-4 under 35 U.S.C. §112, first paragraph, for introducing new matter. Applicants respectfully submit that the present claims are fully supported by the specification.

The Office Action alleges at page 5 that the specification "does not clearly envision the use of probes of different concentration for a single loc[us]." However, the claims do not require "different concentration for a single loc[us]," as the Office Action alleges. The claims require "at least two of the plurality of molecular inversion probes are present at different concentrations in the probe set."

The specification supports at least two of the plurality of molecular inversion probes being present at different concentrations in the probe set. For example, the specification states, "the amount of probe used per assay may be optimized for a particular application." Application, page 70, lines 7-8. The "optimization" includes adjusting the "ratio (molar ratio, for example measured as a concentration ratio) of probe." *Id.* at 70, lines 8-9.

The Office Action at page 5 even concedes that "the specification teaches varying the concentration of probes between different loci."

Accordingly, the present claim, which recites "at least two of the plurality of molecular inversion probes are present at different concentrations in the probe set," is supported by the specification. Applicants submit that the rejection under 35 U.S.C. §112, first paragraph, is overcome.

Rejection under 35 U.S.C. §112, second paragraph

The Office Action rejects claims 1-4 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite. However, in making that rejection, the Office Action ignores the amendments and arguments made in the response of September 14, 2015. That response (at pages 9-10) addresses each and every indefiniteness rejection.

The Office Action at pages 7-10 merely reiterates the rejection of an earlier version of the claims, which is not relevant here. The present Office Action raises no rejections under 35 U.S.C. §112, second paragraph, that are applicable to the presently pending claims. Applicants therefore submit that the rejection is moot.

Since the rejection is not applicable to the presently pending claim set, Applicants submit that the rejection is moot and should be withdrawn.

Rejections under 35 U.S.C. §103

The Office Action maintains the rejections of claims 1-4 under 35 U.S.C. §103(a) over the combination of Akhras (PLOS one, 2007, 2(9):e915), Nilsson (Trends in Biotechnology, 2006, 24:83-88), Hardenbol (Nature Biotechnology, 2003, 21:673-78), Mockler (Genomics, 2005, 85:1-15), Porreca (Nature Methods, 2007, 4:931-36), Hardenbol (2006/0019304), and Browne (2006/0246500). Applicants submit that the present claims are not made obvious by any combination of those references.

The present claims require that at least two of the plurality of molecular inversion probes are present at different concentrations in the probe set. Using probes of different concentrations in a single assay helps to reduce bias. *See* Application, page 67-70. None of the cited references discloses or suggests reducing bias using different concentrations of probes in a single assay.

Akhras, Nilsson, Hardenbol (2003), and Mockler are all limited to reporting the use of padlock probes or general tiling strategies. The three references that the Office Action alleges report "probes at two or more concentrations" are Porreca, Hardenbol (2006), and Browne.

However, Applicants submit that none of those references teaches probes at two or more

concentrations in the same reaction. Since none of the cited references reports probes at two or more concentrations in the same reaction, no combination of the references teaches that either.

Porreca reports a method for gene amplification using molecular inversion probes. *See* Porreca, page 932, col 1, lines 11-25. Porreca notes that some base calls were skewed away from the expected 50:50 ratio. Porreca suggests solving that problem by saturating the reaction mixture with an excess of all reactants and not by using different probe concentrations. *Id.* at 934, col 2, lines 30-59. At page 16, the Examiner refers to Porreca's statement that "[i]f either the targeting oligos or genomic DNA can be defined as limiting, one could potentially hybridize with an excess of the complement, that is, to saturation, such that small differences in capture efficiency would be 'normalized' away." Again Porreca describes saturating the reaction mixture with either excess probe or excess genomic DNA rather than having two different probe concentrations.

Hardenbol (2006) addresses concentration as a factor in hybridization assay design. *See, e.g.,* Hardenbol (2006), paragraphs [0038] and [0048]. Hardenbol (2006) mentions probe concentration as a standard parameter in a hybridization assay, but never discloses or suggests using two different probe concentrations in an assay. The protocols described do not contemplate varying probe concentration to account for biases due to alleles bring present at ratios other than 50:50. Accordingly, Hardenbol (2006) cannot properly be read to disclose or suggest using different probe concentrations in a reaction to address the problem of bias occurring at loci with alleles having ratios that deviate from 50:50.

On page 16, the Examiner points to a passage in Hardenbol (2006) related to probe concentration: "at a given probe concentration there is a finite rate at which the probe sequences will hybridize to the genomic templates. Probe concentrations can be adjusted to some extent to vary this rate." However, that passage merely reports adjusting the concentration of probe to vary the hybridization rate. It fails to say anything about varying concentration between two probes in a reaction.

On page 17, the Examiner points to a passage in Hardenbol that states: "[t]he number of

loci in each hybridization-based assay can vary widely, and its upper limit depends on well-known factors, including . . . probe concentrations." Again, that passage fails to disclose varying concentrations between two probes in a reaction. Instead, that passage is about varying concentrations between different assays. The Examiner fails to distinguish adjusting concentrations among different assays from varying probe concentrations within an assay. The Examiner at pages 17-18 further points to a passage of Hardenbol that states:

> Usually there is a one-to-one correspondence between the number of hybridization-based assay products combined in accordance with the invention and the number of different genomic samples being analyzed; however, the invention comprehends situations where different numbers of samples from different individuals are analyzed by varying numbers of hybridization-based assays, the products of which are combined. The level of such multiplexing depends on the capacity of the readout device and the number of loci measured by each hybridization-based assay.

Once again, that passage fails to disclose two or more probe concentrations in a single assay. Instead, that passage indicates that often each sample being analyzed in a multiplex assay has a set of assay products associated with it. Hardenbol merely notes that an assay can be performed that combines a different number of samples and hybridization-based assay products (i.e., not the same number as each other). In other words, a set of assay products can analyze two or more different samples and therefore the assay can have a different number of samples and hybridization-based assay products. But that passage in no way reports different concentrations between two probes in an assay.

The Office Action alleges that Browne demonstrates dual inversion probes at different concentrations in FIG. 6. However, Browne FIG. 6 merely shows the results of a series of separate and discrete assays, each using different probe concentrations. *See* Browne, paragraph [0114]. For any single assay in Browne, the probe concentrations are the same. Browne does not disclose or suggest an assay using different probe concentrations in the same assay. Browne would have no reason to report more than one probe concentration in a single assay because Browne is not concerned with controlling for bias. Instead, Browne is interested in probe

concentration merely to minimize signal-to-noise ratio in fluorescent probe hybridization assays. Browne is attempting to control background fluorescence, not accounting for biases resulting from allele fractions that are not 50:50.

Accordingly, Porreca, Hardenbol (2006), and Browne fail to disclose or suggest probes at two or more concentrations in the same reaction. The Examiner alleges that using two or more probe concentrations is "merely using known methods to optimize conditions," and yet fails to cite any reference that discloses or suggests using two or more probe concentrations.

Because all of the cited references report using only one concentration of probes in a reaction, there is no motivation to modify by using different concentrations of probes, as is required by the present claims. Therefore, no combination of those references makes the claims obvious.

Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103(a).

Summary

On the basis of the foregoing reasons, Applicants respectfully submit that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative.

Dated: April 21, 2016

Respectfully submitted,
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Petitioner Illumina, Inc., EX1002, p. 1111

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	GSGE-002/01US 29258/20	6082

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
06/10/2016	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):

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Office Action Summary	Application No. 13/266,862	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 *4/21/2016*.

☐ 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) *1-4,12-16,20-30,33,36-38,40-47 and 50-56* is/are pending in the application.

5a) Of the above claim(s) *12-16,20-30,33,36-38,40-47 and 50-56* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-4* 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 *4/8/2013* 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.

Claim Status and Formal matters

This action is in response to papers filed 4/21/2016.

Claims 1-4, 12-16, 20-30, 33, 36-38, 40-47 and 50-56 are pending.

Claims 5-11, 17-19,31-32, 34-35, 39-38, 48-49 and 57-67 have been canceled.

Claims 12-16, 20-30, 33, 36-38, 40-47 and 50-56 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention , there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/3/2012.

Claims 1-4 are being examined.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied

with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the first paragraph of pre-AIA 35 U.S.C. 112, except for the best mode requirement. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994)

The disclosure of the prior-filed application, Application Nos. 61/174,470, 61/174,923, 61/179,358, 61/182, 089, fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph for one or more claims of this application. Application Nos. 61/174,470, 61/174,923, 61/179,358, 61/182, 089, fail to provide support for, “wherein at least two of the plurality of molecular inventions probes are present at different concentrations. “Thus the instant claims are being given priority to 4/30/2010. The filing date of the instant application as a PCT.

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 1-4 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 at least two of the plurality of molecular inversion probes are present at different concentrations. " The response asserts the amendment is supported on pages 69 line 28 to page 70 line 23 which states:

> 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, 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.

The specification teaches on page 3, “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.”

Thus the specification teaches varying the concentration of probes between different loci, but does not clearly envision the use of probes of different concentration for a single loci as the active steps of the claims suggest. Thus the amendment has introduced new matter.

Response to Arguments

The response traverses the rejection asserting, “The Office Action alleges at page 5 that the specification "does not clearly envision the use of probes of different concentration for a single loc[us]." However, the claims do not require "different concentration for a single loc[us]," as the Office Action alleges. The claims require "at least two of the plurality of molecular inversion probes are present at different concentrations in the probe set."." This argument has been thoroughly reviewed but is

not considered persuasive as the probes are drawn to "the target nucleic acid." Thus the claims do require a plurality of probes to a single locus or "the target nucleic acid."

The response continues by providing citing portions of the specification which have been previously reviewed and are not persuasive for the reasons of record.

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 1-4 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 1 further recites, “the 5' region and 3' region being complementary to nucleic acids flanking one of a plurality of subregions of the target nucleic acid.” The

claim appears to require a single target nucleic acid, but sequences to "nucleic acids flanking one of a plurality of subregions." Thus the metes and bounds of the claim are unclear if there is a single target nucleic acid to which the molecular inversion probe is being hybridized or if the intent is the 3' region and 5' region of each probe is hybridizing to a different nucleic acid. The claims should be amended to clarify the relationship between the 3' region and 5' region of the probes as to whether they are hybridizing a single target polynucleotide or different nucleic acids.

Thus claims 2-4 are rejected as they depend from claim 1.

Claim 2 requires, "wherein at least one subregion entirely overlaps at least one other subregion." Claim 1 requires, "the 5' region and 3' region being complementary to nucleic acids flanking one of a plurality of subregions of the target nucleic acid, wherein the subregions of the target nucleic acid are different, wherein each subregion overlaps with at least one other subregion,." Thus it is unclear how one subregion can entirely overlap as required by claim 2 and yet be different as required in claim 1. Thus the metes and bounds of the claim are unclear.

Response to Arguments

The response provides no specific arguments with respect to the 112-2nd paragraph rejections.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 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 of this title, 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.

8. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akhras et al (PLOS one (2007) volume 2 (9) e915) (IDS 3/28/2013), Nilsson et al (Trends in Biotechnology (2006) volume 24, pages 83-88), Hardenbohl et al (Nature Biotechnology(2003) volume 21, pages 673-678), Mockler et al (Genomics (2005) volume 85, pages 1-15), Porecca et al (Nature methods (2007) volume 4, pages 931-936), Hardenbohl et al (USPGPUB 2006/0019304) and Browne et al (US PGPUB 20060246500).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

It is further noted the 112-2nd issues are considered in rendering this rejection.

Akhras teaches a connector inversion probe method (CIPer) that is a combination of Gap-LCR and padlock probes. Akhras teaches, “The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay [17], which includes: i) probe hybridization, single “G” base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by re-linearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target.” Akhaus further teaches, " Connector Inversion Probe (CIPer) technology is a powerful method for multiplex amplification, and has been validated here in genetic pathogen diagnostics, typing, and antibiotic resistance detection arenas as a proof-of-concept. This technology can be designed and optimized for use in numerous other scientific areas and applications. Other areas suitable for use of the CIPer method include cancer genomics [32], human SNP detection [15], and selective exon amplification [7], among numerous other promising applications. Modified CIPers may also in the future offer an alternative strategy for gateway cloning [33]. In this paper, we focused on “lowplex” systems amplifying shorter stretches of DNA of up to 100 base pair lengths. To achieve higher degrees of multiplexing and longer clone reads, one must take into account i) clone GC content, ii) clone length variability, and iii) steric effects for longer clones. Analog amplification and downstream validation are delimiting factors for multiplex detection methods. We believe that the future of CIPer technology will rely on digital amplification [34] and high throughput sequencing validation (Figure

S5). The CIPers universal primer sites can be formatted to fit any amplification method, e.g. RCA [12], [13], emulsion PCR [34], SPIA [35] LAMP [36] and SMAP 2 [37]; universal adaptor ligation, a tedious and sample-consuming procedure [38], is therefore optional. Proposed digital amplification methods include emulsion PCR, RCA, or a combination of the two [39]. Suitable upcoming high throughput validation methods include next-generation sequence systems such as the 454 Life Sciences platform [38] (http://www.454.com), the Solexa platform [40] (http://www.illumina.com), polony sequencing [41] (http://www.agentcourt.com), Helicos Biosciences [42] (http://www.helicosbio.com), or use of a resequencing array (GeneChip CustomSeq, www.affymetrix.com). Recent digital quantification methods [43] open the possibility for quantitative CIPer technology. With the addition of a molecular barcode to the padlocks [14], MIPs were used for ultra high-throughput SNP detection based on microarray barcode hybridization [15]. Because CIPers can also include a barcode, they could be used for microarray validation, or amplicon tracing with sequencing methods [17], [44] allowing for longer read lengths [38]. With the introduction of a third universal sequence flanking the barcode and the universal primer sites, one can begin to envision a two-dimension informational barcode, a concept we call “multiplexing multiplex padlocks” (MMP) (Figure S6). Probe construction based on ligation of three smaller constructs [45] would allow for variability in fragment assembly. By combining the one-genotype detection pair of AS/ES constructs with multiple unique barcodes, we can create patient and genotype specific probes with one barcode per probe. This will allow for analysis of

multiple parallel samples, essentially lowering the cost of microarray chips and sequencing reactions."

Nilsson teaches the use of padlock probes and "selector" probes that form circles with gaps of several nucleotides between the 5' terminal nucleotide and the 3' terminal nucleotide.

Akhras and Nilsson demonstrate probes were known that result in a circular probe upon hybridization to a target sequence with a gap between the 3' terminal nucleotide and 5' terminal nucleotide were known. Akhras suggests the use of CIPer methods similar to the use of MIPs, including the use of "barcodes to allow detection by microarrays."

Akhras and Nilsson do not specifically teach, "contacting each of a plurality of target nucleic acids with a plurality of different molecular inversion probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids flanking one of a plurality of subregions of the target nucleic acid, wherein the subregions of the target nucleic acid are different, wherein each subregion overlaps with at least one other subregion."

However, Hardenbohl discloses a method of analyzing a plurality of genetic loci by contacting each of a plurality of target nucleic acids with a probe set (abstract, pg 673, col 2, para 2, Fig. 2; pg 674, col 2, para 3-1,517 loci were genotyped in a 1,517-probe multiplex analysis), 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 (Fig. 2a, b; pg 674, col 2, para 3), wherein the subregions of the target nucleic acid are different (pg 674, col 2, para 2-3--probes were generated for 1,121 SNPs. 1,517 loci were genotyped in a 1,517-probe multiplex analysis), 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 (pg 674, col 1, para 2 to pg 674, col 2, para 1). Hardenbohl teaches these probes are MIP or padlock probes.

Hardenbohl teaches in figure 2b the joining of the molecular inversion probes which results in a circular type configuration. Hardenbohl exemplifies in fig 2b a probe that has a 5' region and a 5' terminal nucleotide, a 3' region and a 3' terminal nucleotide, and a single base gap. Thus the 5' terminal nucleotide, 3' terminal nucleotide and single base gap are a plurality of nucleotides between the 3' and 5' region of the probe.

Hardenbohl does not specifically teach wherein each subregion overlaps with at least one other subregion. Hardenbohl does not specifically teach, "wherein at least one subregion entirely overlaps at least one subregion."

Mockler, teaches each subregion overlaps with at least one other subregion (Fig. 2a).

With regards to claim 2, Mockler further teaches wherein at least one subregion entirely overlaps at least one other subregion (Fig. 2D-probes tiled at 1 base resolution (if these were MIPs, as taught by Hardenbol, at least two of the nucleotides would be flanking nucleotides and thus one subregion would entirely overlap one other

Subregion)).

With regards to claim 3, Mockler teaches 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 (Fig. 2B).

With regards to claim 4, Mockler teaches 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 (Fig. 2a-H1 and H2 unique to each probe).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the CIPer or selector probes taught by Akhras and Nilsson with a gap of a plurality of nucleotides between the 5’ terminal nucleotide and 3’ terminal of the padlock probes with tiling probes of Mockler in the method of Hardenbol. The artisan would be motivated as Akhras suggests the use of CIPer methods in MIP methods. The teachings of Hardenbohl set forth one embodiment of the use of MIP or padlock probes. The artisan further would be motivated as Mockler teaches the probe tiling approach reduces bias (pg 2, col 1, para 4 to pg 2, col 2, para 1). The artisan would have a reasonable expectation of success as the artisan is merely increasing the number of nucleotides between the 3’ terminal nucleotide and 5’ terminal nucleotide of the probes of Mockler, which Akhras demonstrates were known and worked. Thus the combination of references suggests all the limitations of claims and suggests the use of CIPer in place of the similar MIP methods.

Akhras, Nilsson, Hardenbohl, and Mockler do not specifically teach the use of probes at two or more concentrations.

However, Porecca teaches a method of amplifying human exons using MIPS. Porecca teaches, “It is both concerning and interesting that the resequencing data show skewing of base-calls at heterozygous positions away from the expected ratio of 0.5 (Fig. 4). This skewing might be expected if stochastic events (for example, a finite number of capture events during the multiplex capture reaction) are a primary source of bias. Given that the concentration of individual targeting oligos in the capture reaction is very low (B0.36 pM per species), it is likely that their hybridization to genomic DNA is inefficient. This problem might therefore be mitigated simply by increasing the concentration of reactants. If either the targeting oligos or genomic DNA can be defined as limiting, one could potentially hybridize with an excess of the complement, that is, to saturation, such that small differences in capture efficiency would be ‘normalized’ away.” Porecca further teaches, “After characterizing the efficiency of individual capture oligos in each reaction, a second iteration could be carried out, in which capture oligos performing similarly to one another are grouped together within the same oligo mixture (thereby maximizing uniformity within any single reaction).”

Further, Hardenbohl(PGPUB) teaches, “Genomic material is complex and thus individual sequences exist at relatively low concentrations in a mixture. As a result of this, at a given probe concentration there is a finite rate at which the probe sequences will hybridize to the genomic templates. Probe concentrations can be adjusted to some extent to vary this rate, but as probe complexity is increased, for example, when highly

multiplexed assays are used, such flexibility is greatly reduced" (003). Hardenbohl continues, "Multiplexing occurs at two levels in the invention. First, hybridization-based assays are designed to measure characteristics of one or more target polynucleotides, such as genomic fragments, at multiple loci. The number of loci measured in each hybridization-based assay can vary widely, and its upper limit depends on well-known factors, including the capacity of the readout device being employed, trade-offs selected between probe concentrations and reaction times, the genetic characteristic being measured (for example, trait association studies require very large numbers of measurements; genetic identification requires relative few measurements; testing for adverse drug reactions may require a medium number of measurements, e.g. several tens to hundreds), and the like. In one aspect, the number of loci analyzed in each hybridization-based assay is in the range of from a few tens, e.g. 10 to 20, to many thousands, e.g. fifty to a hundred thousand. In another aspect, the number of loci per hybridization-based assay is in the range of from 10 to 40,000; or it is in the range of from 100 to 30,000; or it is in the range of from 100 to 20,000. Second, multiplexing occurs from the combination of assay products from multiple hybridization-based assays for determining multiple signals on a single readout device. Usually, there is a one-to-one correspondence between the number of hybridization-based assay products combined in accordance with the invention and the number of different genomic samples being analyzed; however, the invention comprehends situations where different numbers of samples from different individuals are analyzed by varying numbers of hybridization-based assays, the products of which are combined. The level

of such multiplexing depends of the capacity of the readout device and the number of loci measured by each hybridization-based assay. In one aspect, the number of hybridization-based assays that may be multiplexed is simply the capacity of a readout device, e.g. the number of features on a microarray, divided by the number of loci being measured in the hybridization-based assays. For example, in one aspect, a 100 thousand-feature microarray can serve as a readout device for fifty hybridization based assays that each measure the zygosity of one thousand loci, when two features are required for each determination (e.g. homozygous in allele 1, homozygous in allele 2, or heterozygous in allele 1 and 2). As discussed more fully below, particular trade-offs between the use of microarray features, different colored fluorescent dyes, number of loci measured per hybridization-based assay, capacity of a readout device, and the like, are routine design choices for those of ordinary skill in the art."

Hardenbohl (PGPUB) continues, "Operation of one embodiment of the invention is illustrated in FIGS. 1A and 1B for a particular hybridization-based assay (one based on the template-driven ligation of two oligonucleotide components). Hybridization-based assays are carried out separately on a sample of DNA from genome G.sub.1 and a sample of DNA from genome G.sub.2. Probes p.sub.1 to p.sub.K (100) containing oligonucleotide tags t.sub.1 to t.sub.K, respectively, and probes p.sub.1 to p.sub.K (102) containing oligonucleotide tags t.sub.K+1 to t.sub.2K, respectively, are combined in separate reaction mixtures with genome G.sub.1 DNA and genome G.sub.2 DNA, respectively, under conditions that permit specific hybridization of such probes to their respective DNA stands (104) and (106) containing target loci, L.sub.1 through L.sub.K

((108) to (110) for genome G.sub.1 and (112) to (114) for genome G.sub.2). After an incubation time depending on parameters well-known to those of ordinary skill, e.g. target complexity, probe concentration, temperature, and the like, discussed more fully below, probe-genome complexes form ((118) and (116), respectively) that include recognition structures for enzyme(s) of subsequent step(s)."

Finally, Browne demonstrates the use of dual inversion probes at different concentrations in figure 6.

As stated in the MPEP, 2144.05 II, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Akhras, Nilsson, Hardenbohl, and Mockler to include at probes at different concentrations in a sample to optimize hybridization and assay conditions in a sample. The artisan would be motivated as Porecca, Hardenbohl(PGPUB), and Brown recognize that probe concentration is an optimizable variable in the speed and performance of hybridization assays including molecular inversion probe assays. Thus it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include additional probes at different concentrations so as to optimize efficiency of hybridization as well as speed of hybridization in a sample. The artisan would have a

reasonable expectation of success as the artisan is merely using known methods to optimize conditions.

Response to Arguments

The response traverses the rejection by providing the representatives interpretation of Akhras, Nilsson, Hardenbol (2003) and Mockler. The response asserts the Akhras, Nilsson, Hardenbol and Mockler do not teach probes at different concentrations. This argument is not considered persuasive as this is consistent with the rejection.

The response traverses the instant rejection asserting, “Porreca reports a method for gene amplification using molecular inversion probes. See Porreca, page 932, col 1, lines 11-25. Porreca notes that some base calls were skewed away from the expected 50:50 ratio. Porreca suggests solving that problem by saturating the reaction mixture with an excess of all reactants. Id. at 934, col 2, lines 30-59. Porreca does not disclose or suggest using different probe concentrations in a single sample.” This argument has been thoroughly reviewed but is not considered persuasive as Porreca teaches, “Given that the concentration of individual targeting oligos in the capture reaction is very low (~ 0.36 pM per species), it is likely that their hybridization to genomic DNA is inefficient. This problem might therefore be mitigated simply by increasing the concentration of reactants. If either the targeting oligos or genomic DNA can be defined as limiting, one could potentially hybridize with an excess of the complement, that is, to saturation, such that small differences in capture efficiency would be 'normalized' away”.(emphasis added by the examiner). Thus Porrecca

suggest that individual targeting oligos may be rate limiting and can be increased. In the context of the paragraph rendering obvious varying conditions of probes. Further this argument is arguing the teachings of Porrecca alone. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The response continues by asserting Hardenbol(2006) does not specifically disclose or suggest probes of different concentration in a sample. This argument has been thoroughly reviewed but is not considered persuasive as Hardenbohl clearly envisions that probe concentration is a hybridization parameter that can be optimized. Further this argument is arguing the teachings of Hardenbohl alone. The response continues by reproducing a portion of Hardenbol cited by the rejection asserting it does not support the obviousness of the rejection. It is noted numerous portiosn of Hardebohl are cited and the full portion cited by the examiner states:

> Multiplexing occurs at two levels in the invention. First, hybridization-based assays are designed to measure characteristics of one or more target polynucleotides, such as genomic fragments, at multiple loci. The number of loci measured in each hybridization-based assay can vary widely, and its upper limit depends on well-known factors, including the capacity of the readout device being employed, trade-offs selected between probe concentrations and reaction times, the genetic characteristic being measured (for example, trait association studies require very large numbers of measurements; genetic identification requires relative few measurements; testing for adverse drug reactions may require a medium number of measurements, e.g. several tens to hundreds), and the like. In one aspect, the number of loci analyzed in each hybridization-based assay is in the range of from a few tens, e.g. 10 to 20, to many thousands, e.g. fifty to a hundred thousand. In another aspect, the number of loci per hybridization-based assay is in the range of from 10 to 40,000; or it is in the range of from 100 to 30,000; or it is in the range of from 100 to 20,000. Second, multiplexing

occurs from the combination of assay products from multiple hybridization-based assays for determining multiple signals on a single readout device. Usually, there is a one-to-one correspondence between the number of hybridization-based assay products combined in accordance with the invention and the number of different genomic samples being analyzed; however, the invention comprehends situations where different numbers of samples from different individuals are analyzed by varying numbers of hybridization-based assays, the products of which are combined. The level of such multiplexing depends of the capacity of the readout device and the number of loci measured by each hybridization-based assay. In one aspect, the number of hybridization-based assays that may be multiplexed is simply the capacity of a readout device, e.g. the number of features on a microarray, divided by the number of loci being measured in the hybridization-based assays. For example, in one aspect, a 100 thousand-feature microarray can serve as a readout device for fifty hybridization based assays that each measure the zygosity of one thousand loci, when two features are required for each determination (e.g. homozygous in allele 1, homozygous in allele 2, or heterozygous in allele 1 and 2). As discussed more fully below, particular trade-offs between the use of microarray features, different colored fluorescent dyes, number of loci measured per hybridization-based assay, capacity of a readout device, and the like, are routine design choices for those of ordinary skill in the art.

Thus the teachings of Hardenbohl, Porrecca and Brown as a whole recognize that probe concentration can be an optimizable condition.

The response continues by asserting Browne does not teach probe concentration is a single assay. This argument has been thoroughly reviewed but is not considered persuasive as the claim does not necessarily require the probes in a single assay, but merely the sample is contacted with probe sets. This could be interpreted as placing portions of the sample with part of the probes. Further the response is again arguing the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection is maintained as the prior art as a whole demonstrates that varying probe concentrations is an optimizable factor in hybridization and specifically in inversion probes. Thus the art recognizes the problem of probe concentration on hybridization and recognizes that varying the probe concentration can be done to improve the results of the assay.

Summary

No claims are allowed.

Conclusion

1. **THIS ACTION IS MADE FINAL.** 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.

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

Electronic Acknowledgement Receipt	
EFS ID:	27166916
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Lauren Poon
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	GSGE-002/01US 29258/20
Receipt Date:	10-OCT-2016
Filing Date:	13-MAR-2012
Time Stamp:	15:44:42
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$950
RAM confirmation Number	11568
Deposit Account	500369
Authorized User	Meyers, Thomas
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 CFR 1.492 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 CFR 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 CFR 1.19 (Document supply fees)

Charge any Additional Fees required under 37 CFR 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 CFR 1.21 (Miscellaneous fees and charges)

Charge any Additional Fees required under 37 CFR 1.492(a) (basic national fee only)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		GSGE-002-01US-Response-to-FOA-061016.pdf	58478 2c7f4a864243fa37076ba3b56f108cf66d5ff71c	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment Submitted/Entered with Filing of CPA/RCE	1	1
Claims	2	8
Applicant Arguments/Remarks Made in an Amendment	9	12

Warnings:

Information:

2	Extension of Time	GSGE-002-01US-EOT.pdf	21680 8831f50dabc1907f50464754e8670c09ef339a41	no	1

Warnings:

Information:

3	Request for Continued Examination (RCE)	GSGE-002-01US-RCE-101016.pdf	3371197 b9af65c32befd044b05256fd70f6931e08fc87e9	no	3

Warnings:

This is not a USPTO supplied RCE SB30 form.

Information:

4	Fee Worksheet (SB06)	fee-info.pdf	32669 f731eb26d2ec296b81fe0e6f18e0621c5c80da16	no	2

Warnings:

Information:

Total Files Size (in bytes):	3484024

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:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	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 the final office action mailed June 10, 2016, from the United States Patent and Trademark Office. Applicants submit herewith a Request for Continued Examination (RCE) and petition for a one-month extension of time. Applicants pay the RCE fee and the extension of time fee. Applicants authorize the Commissioner to charge any other required fee to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 9.

Amendment to the claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently Amended) 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; and

a central region flanked by the 5' region and the 3' region;

wherein the 5' region ~~and 3' region of each probe are~~ is complementary to a nucleic acid residue[[s]] flanking ~~the same strand of~~ 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; and

wherein 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; ~~and~~

~~wherein at least two of the plurality of molecular inversion probes are present at different concentrations in the probe set;~~

converting hybridized probes into closed circularized probes;

isolating a plurality of circularized probes having nucleic acid sequences of different subregions; and

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analyzing the isolated subregions.

2. (Canceled)

3. (Original) 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. (Original) 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.

5-11. (Canceled)

12. (Withdrawn) 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. (Withdrawn) 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.

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14. (Withdrawn) The method of claim 12, 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. (Withdrawn) The method of claim 12, wherein the threshold number for a specific target nucleic acid sequence is selected based on a desired statistical confidence for the genotype.

16. (Withdrawn) The method of claim 12, further comprising determining a statistical confidence for the genotype based on the number of unique combinations of target nucleic acid and differentiator tag sequences.

17-19. (Canceled)

20. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 20, wherein the capture efficiency is lower than the reference capture efficiency.

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

24. (Withdrawn) The method of claim 20, wherein the capture efficiency is higher than the reference capture efficiency.

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

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

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

28. (Withdrawn) The method of claim 20, wherein a sub-target nucleic acid is captured from the target nucleic acid using a molecular inversion probe.

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

31-32. (Canceled)

33. (Withdrawn) The method of claim 29, wherein the first and second targeting arms have the same length.

34-35. (Canceled)

36. (Withdrawn) The method of claim 29, wherein the hybridization Tms of the first and second targeting arms are identical.

37. (Withdrawn) The method of claim 28, wherein the sub-target nucleic acid contains a nucleic acid repeat.

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

39. (Canceled)

40. (Withdrawn) 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. (Withdrawn) The method of claim 29, 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.

Petitioner Illumina, Inc., EX1002, p. 1143

42. (Withdrawn) The method of claim 29, 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. (Withdrawn) The method of claim 29, 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. (Withdrawn) The method of claim 20, wherein a plurality of different target nucleic acids are analyzed in a biological sample.

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

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

48-49. (Canceled)

50. (Withdrawn) The method of claim 20, wherein the capture efficiency is evaluated by determining an amount of target nucleic acid that is captured.

51. (Withdrawn) 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.

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

53. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 20, 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.

57-67. (Canceled)

Remarks

Claims 1, 3, and 4 are pending in the application. Claim 1 is amended to incorporate subject matter from claim 2 and to address the new matter rejection discussed below. Claim 2 is canceled. No new matter is added.

Rejection under 35 U.S.C. §112, first paragraph

The Office Action rejects claims 1-4 under 35 U.S.C. §112, first paragraph, for introducing new matter. In particular, the Office Action alleges that the specification does not teach at least two of the plurality of molecular inversion probes being present at different concentrations in the probe set. Applicants maintain that the specification does support that element. However, merely for the purpose of advancing prosecution, Applicants hereby amend the claims to remove the rejected language. Applicants submit that the rejection under 35 U.S.C. §112, first paragraph, is overcome.

Rejection under 35 U.S.C. §112, second paragraph

The Office Action rejects claims 1-4 under 35 U.S.C. §112, second paragraph, for being indefinite. In particular, the Office Action alleges that it is unclear "if there is a single target nucleic acid to which the molecular inversion probe is being hybridized or if the intent is the 3' region and 5' region of each probe is hybridizing to a different nucleic acid."

Claim 1 is amended to clarify that each of the 3' region and the 5' region hybridizes to a different nucleic acid region, each of which flanks the subregion of interest. Applicants submit that the amended claims overcome the indefiniteness rejection.

Rejections under 35 U.S.C. §103

The Office Action maintains the rejections of claims 1-4 under 35 U.S.C. §103(a) over the combination of Akhras (PLOS one, 2007, 2(9):e915), Nilsson (Trends in Biotechnology, 2006, 24:83-88), Hardenbol (Nature Biotechnology, 2003, 21:673-78), Mockler (Genomics,

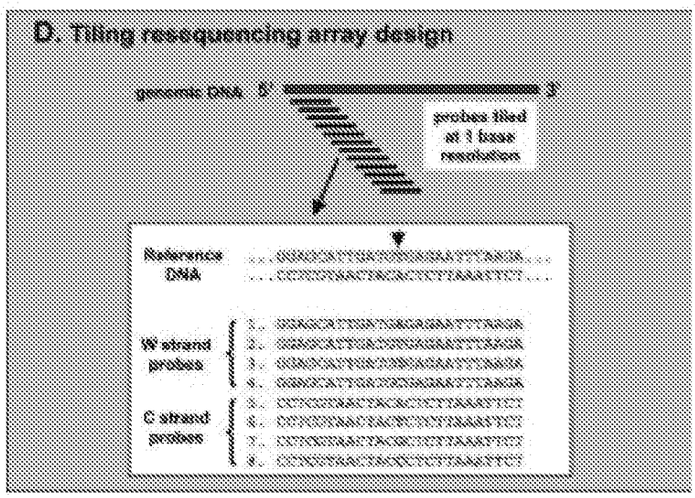
2005, 85:1-15), Porreca (Nature Methods, 2007, 4:931-36), Hardenbol (2006/0019304), and Browne (2006/0246500). Applicants submit that the present claims are not made obvious by any combination of those references.

The present claims require molecular inversion probes configured to capture a plurality of subregions, wherein each subregion overlaps with at least one other subregion; and wherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence. As explained in the specification at page 35, lines 3-15, the set of molecular inversion probes can be designed to "stagger" the exact positions of the hybridization regions (i.e., the 5' region and the 3' region) flanking the target. That allows the MIPs to capture the full target with multiple probes having different targeting arms. Since all MIPs in the set are different, this variability in targeting arms solves problems associated with inefficient probe hybridization. *See id., page 34, lines 30-32.*

None of the prior art references discloses or suggests a set of molecular inversion probes in which one probe is designed to capture a subregion that entirely overlaps another subregion and captures additional flanking sequence.

As stated above, claim 1 has been amended to incorporate the subject matter from claim 2. With respect to claim 2, Mockler is the only reference that the Office Action alleges shows that element. However, Applicants disagree with the interpretation of Mockler.

Mockler reports various probe tiling strategies in FIGS. 2A-D. None of the tiling strategies include one probe that captures a subregion that entirely overlaps another subregion and captures additional flanking sequence. The embodiment that the Office Action points to is in FIG. 2D, reproduced below.



As shown in FIG. 2D, the probes are tiled at 1-base resolution, meaning that no subregion entirely overlaps another subregion. The Office Action however states that if the probes were MIPs, "at least two of the nucleotides would be flanking nucleotides and thus one subregion would entirely overlap one other subregion." Applicants disagree. First, the 3' and 5' regions target nucleic acids that flank the subregion, and so the subregion as defined in claim 1 does not include the flanking sequences. The tiling design in Mockler therefore does not disclose the presently claimed method. Second, even if it was assumed that the flanking regions were included in the "subregion," no subregion shown in FIG. 2D would overlap any other subregion in its entirety because, by that logic, each of the subregions would have to be altered by the length of the MIPs. There is simply no way to interpret the tiling design of FIG. 2D, which shows probes tiled at 1-base resolution, to mean that any subregion entirely overlaps another.

No other reference is alleged to show that element, and so no combination of the references makes the present claims obvious. Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103(a).

Summary

On the basis of the foregoing reasons, Applicants respectfully submit that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions

regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative.

Dated: October 10, 2016

Respectfully submitted,
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PTO/SB/22 (03-13)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) GSGE-002/01US 29258/20
Application Number 13/266862	Filed March 13, 2012
For METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS	
Art Unit 1634	Examiner S. C. Pohnert

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
[X] One month (37 CFR 1.17(a)(1))	$200	$100	$50	$ 100.00
[ ] Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
[ ] Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$
[ ] Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
[ ] Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

[X] Applicant asserts small entity status. See 37 CFR 1.27.

[ ] Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

[ ] A check in the amount of the fee is enclosed.

[ ] Payment by credit card. Form PTO-2038 is attached.

[X] The Director has already been authorized to charge fees in this application to a Deposit Account.

[X] The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-0369 .

[X] Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

[ ] applicant/inventor.

[ ] assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

[X] attorney or agent of record. Registration number 36,989 .

[ ] attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Thomas C. Meyers/	October 10, 2016
Signature	Date
Thomas C. Meyers	(617) 856-8200
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

[ ] * Total of 1 forms are submitted.

PTO/SB/30 (07-14)
Approved for use through 07/31/2016 OMB 0651-0031
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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

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

Application Number	13/266862
Filing Date	March 13, 2012
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	Steven C. Pohnert
Attorney Docket Number	GSGE-002/01US 29258/20

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, to any international application that does not compy with the requirements of 35 U.S.C 371, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO on page 2.)

1. 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).

   a. ☐ 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.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ 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)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 50-0369 .

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Thomas C. Meyers/	Date	October 10, 2016
Name (Print/Type)	Thomas C. Meyers	Registration No.	36989

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature			
Name (Print/Type)		Date	

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. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, 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/SB/30 (07-14)
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Instruction Sheet for RCEs

(not to be submitted to the USPTO)

NOTES:

An RCE is not a new application, and filing an RCE will not result in an application being accorded a new filing date.

Filing Qualifications:

The application must be a utility or plant application filed on or after June 8, 1995. The application cannot be a provisional application, a utility or plant application filed before June 8, 1995, an international application that does not comply with the requirements of 35 U.S.C. 371, a design application, or a patent under reexamination. See 37 CFR 1.114(e). An international application does not comply with the requirements of 35 U.S.C. 371 until the requirements under 35 U.S.C. 371(c), including the requirement for the inventor's oath or declaration under 35 U.S.C. 371(c)(4), have been complied with.

Filing Requirements:

Prosecution in the application must be closed. Prosecution is closed if the application is under appeal, or the last Office action is a final action, a notice of allowance, or an action that otherwise closes prosecution in the application (e.g., an Office action under *Ex parte Quayle*). See 37 CFR 1.114(b).

A submission and a fee are required at the time the RCE is filed. If reply to an Office action under 35 U.S.C. 132 is outstanding (e.g., the application is under final rejection), the submission must meet the reply requirements of 37 CFR 1.111. If there is no outstanding Office action, the submission can be an information disclosure statement, an amendment, new arguments, or new evidence. See 37 CFR 1.114(c). The submission may be a previously filed amendment (e.g., an amendment after final rejection).

WARNINGS:

Request for Suspension of Action:

All RCE filing requirements must be met before suspension of action is granted. A request for a suspension of action under 37 C FR 1.103(c) does not satisfy the submission requirement and does not permit the filing of the required submission to be suspended.

Improper RCE will NOT toll Any Time Period:

Before Appeal - If the RCE is improper (e.g., prosecution in the application is not closed or the submission or fee has not been filed) and the application is not under appeal, the time period set forth in the last Office action will continue to run and the application will be abandoned after the statutory time period has expired if a reply to the Office action is not timely filed. No additional time will be given to correct the improper RCE.

Under Appeal - If the RCE is improper (e.g., the submission or the fee has not been filed) and the application is under appeal, the improper RCE is effective to withdraw the appeal. Withdrawal of the appeal results in the allowance or abandonment of the application depending on the status of the claims. If there are no allowed claims, the application is abandoned. If there is at least one allowed claim, the application will be passed to issue on the allowed claim(s). See MPEP 1215.01.

See MPEP 706.07(h) for further information on the RCE practice.

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.

Electronic Patent Application Fee Transmittal	
Application Number:	13266862
Filing Date:	13-Mar-2012
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Lauren Poon
Attorney Docket Number:	GSGE-002/01US 29258/20
Filed as Small Entity	
Filing Fees for U.S. National Stage under 35 USC 371	

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 $0 paid	2251	1	100	100
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	850	850
		Total in USD ($)		**950**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	GSGE-002/01US 29258/20	6082

21710 7590 03/16/2017

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
03/16/2017	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. 13/266,862	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 *10/10/2016*.

☐ 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) *1,3,4,12-16,20-30,33,36-38,40-47 and 50-56* is/are pending in the application.

5a) Of the above claim(s) *12-16,20-30,33,36-38,40-47 and 50-56* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3 and 4* 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 *4/8/2013* 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.

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 10/10/2016 has been entered.

Claim Status and Formal matters

This action is in response to papers filed 10/10/2016.

Claims 1, 3-4, 12-16, 20-30, 33, 36-38, 40-47 and 50-56 are pending.

Claims 2, 5-11, 17-19, 31-32, 34-35, 39-38, 48-49 and 57-67 have been canceled.

Claims 12-16, 20-30, 33, 36-38, 40-47 and 50-56 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention , there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/3/2012.

Claims 1, 3-4 are being examined.

Claim 1 has been amended.

The previous new matter rejection has been withdrawn in view of the amendment to delete the pervious terms at issue.

The previous 112-2nd rejection has been withdrawn in view of the amendment.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the first paragraph of pre-AIA 35 U.S.C. 112, except for the best mode requirement. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994)

The disclosure of the prior-filed application, Application Nos. 61/174,470, 61/174,923, 61/179,358, 61/182, 089, fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph

for one or more claims of this application. Application Nos. 61/174,470, 61/174,923, 61/179,358, 61/182, 089, fail to provide support for, “wherein the 5' region is complementary to a nucleic acid residue flanking 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. “Thus the instant claims are being given priority to the filing of the instant 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 1, 3-4 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 the 5' region is complementary to a nucleic acid residue flanking 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. “ The response provides no indication where support for the amendment can be found. Searching and review of the specification for residue are limited to “residues” and are set forth with respect to amino acid (glycine and Lysine) or LNA probes. The specification and claims previously filed do not support a 5’ region and 3' region being complementary to a single nucleotide. Thus the amendment has provided a species that was not envisioned at time of filing.

Response to Arguments

This is a new ground of rejection necessitated by amendment.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 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 of this title, 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.

6. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akhras et al (PLOS one (2007) volume 2 (9) e915) (IDS 3/28/2013), Nilsson et al (Trends in Biotechnology (2006) volume 24, pages 83-88), Hardenbohl et al (Nature Biotechnology(2003) volume 21, pages 673-678), Mockler et al (Genomics (2005) volume 85, pages 1-15), Porecca et al (Nature methods (2007) volume 4, pages 931-

936), Hardenbohl et al (USPGPUB 2006/0019304) and Browne et al (US PGPUB 20060246500).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

Claim 1 has been amended to recite, "wherein the 5' region is complementary to a nucleic acid residue flanking 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." Thus a region a region encompasses a single nucleotide. Thus a subregion logically also encompasses a single nucleotide.

Further the claim has been amended to recite, "wherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence." First it is noted the subregion is a reference to the target nucleic acid and

not the probe. Thus the wherein clause encompasses an intended outcome that is based on the target nucleic acid and not necessarily the probe. Alternatively the claims encompass any probe that has a subregion (nucleotide) that overlaps at least one other subregion (nucleotide) on another probe as a region is a nucleotide.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) “adapted to” or “adapted for” clauses;

(B) “wherein” clauses; and

(C) “whereby” clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a “wherein” clause limited a process claim where the clause gave “meaning and purpose to the manipulative steps”). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a “‘whereby’ clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.” Id. However, the court noted (quoting Minton v. Nat’l Ass’n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a “‘whereby clause in a

method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Akhras teaches a connector inversion probe method (CIPer) that is a combination of Gap-LCR and padlock probes. Akhras teaches, "The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay [17], which includes: i) probe hybridization, single "G" base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by re-linearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target." Akhaus further teaches, " Connector Inversion Probe (CIPer) technology is a powerful method for multiplex amplification, and has been validated here in genetic pathogen diagnostics, typing, and antibiotic resistance detection arenas as a proof-of-concept. This technology can be designed and optimized for use in numerous other scientific areas and applications. Other areas suitable for use of the CIPer method include cancer genomics [32], human SNP detection [15], and selective exon amplification [7], among numerous other promising applications. Modified CIPers may also in the future offer an alternative strategy for gateway cloning [33]. In this paper, we focused on "lowplex" systems amplifying shorter stretches of DNA of up to 100 base pair lengths. To achieve higher degrees of multiplexing and longer clone reads, one must take into account i) clone GC content, ii) clone length variability, and iii) steric effects for longer clones. Analog amplification and downstream validation are delimiting

factors for multiplex detection methods. We believe that the future of CIPer technology will rely on digital amplification [34] and high throughput sequencing validation (Figure S5). The CIPers universal primer sites can be formatted to fit any amplification method, e.g. RCA [12], [13], emulsion PCR [34], SPIA [35] LAMP [36] and SMAP 2 [37]; universal adaptor ligation, a tedious and sample-consuming procedure [38], is therefore optional. Proposed digital amplification methods include emulsion PCR, RCA, or a combination of the two [39]. Suitable upcoming high throughput validation methods include next-generation sequence systems such as the 454 Life Sciences platform [38] (http://www.454.com), the Solexa platform [40] (http://www.illumina.com), polony sequencing [41] (http://www.agentcourt.com), Helicos Biosciences [42] (http://www.helicosbio.com), or use of a resequencing array (GeneChip CustomSeq, www.affymetrix.com). Recent digital quantification methods [43] open the possibility for quantitative CIPer technology. With the addition of a molecular barcode to the padlocks [14], MIPs were used for ultra high-throughput SNP detection based on microarray barcode hybridization [15]. Because CIPers can also include a barcode, they could be used for microarray validation, or amplicon tracing with sequencing methods [17], [44] allowing for longer read lengths [38]. With the introduction of a third universal sequence flanking the barcode and the universal primer sites, one can begin to envision a two-dimension informational barcode, a concept we call “multiplexing multiplex padlocks” (MMP) (Figure S6). Probe construction based on ligation of three smaller constructs [45] would allow for variability in fragment assembly. By combining the one-genotype detection pair of AS/ES constructs with multiple unique barcodes, we can create patient

and genotype specific probes with one barcode per probe. This will allow for analysis of multiple parallel samples, essentially lowering the cost of microarray chips and sequencing reactions."

Nilsson teaches the use of padlock probes and "selector" probes that form circles with gaps of several nucleotides between the 5' terminal nucleotide and the 3' terminal nucleotide.

Akhras and Nilsson demonstrate probes were known that result in a circular probe upon hybridization to a target sequence with a gap between the 3' terminal nucleotide and 5' terminal nucleotide were known. Akhras suggests the use of CIPer methods similar to the use of MIPs, including the use of "barcodes to allow detection by microarrays."

Akhras and Nilsson do not specifically teach, "contacting each of a plurality of target nucleic acids with a plurality of different molecular inversion probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids flanking one of a plurality of subregions of the target nucleic acid, wherein the subregions of the target nucleic acid are different, wherein each subregion overlaps with at least one other subregion."

However, Hardenbohl discloses a method of analyzing a plurality of genetic loci by contacting each of a plurality of target nucleic acids with a probe set (abstract, pg 673, col 2, para 2, Fig. 2; pg 674, col 2, para 3-1,517 loci were genotyped in a 1,517-probe multiplex analysis), 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 (Fig. 2a, b; pg 674, col 2, para 3), wherein the subregions of the target nucleic acid are different (pg 674, col 2, para 2-3--probes were generated for 1,121 SNPs. 1,517 loci were genotyped in a 1,517-probe multiplex analysis), 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 (pg 674, col 1, para 2 to pg 674, col 2, para 1). Hardenbohl teaches these probes are MIP or padlock probes.

Hardenbohl teaches in figure 2b the joining of the molecular inversion probes which results in a circular type configuration. Hardenbohl exemplifies in fig 2b a probe that has a 5' region and a 5' terminal nucleotide, a 3' region and a 3' terminal nucleotide, and a single base gap. Thus the 5' terminal nucleotide, 3' terminal nucleotide and single base gap are a plurality of nucleotides between the 3' and 5' region of the probe.

Hardenbohl does not specifically teach wherein each subregion overlaps with at least one other subregion. Hardenbohl does not specifically teach, "wherein at least one subregion entirely overlaps at least one subregion."

Mockler, teaches each subregion overlaps with at least one other subregion (Fig. 2a).

With regards to claim 2, Mockler further teaches wherein at least one subregion entirely overlaps at least one other subregion (Fig. 2D-probes tiled at 1 base resolution

(if these were MIPs, as taught by Hardenbol, at least two of the nucleotides would be flanking nucleotides and thus one subregion would entirely overlap one other Subregion)).

With regards to claim 3, Mockler teaches 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 (Fig. 2B).

With regards to claim 4, Mockler teaches 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 (Fig. 2a-H1 and H2 unique to each probe).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the CIPer or selector probes taught by Akhras and Nilsson with a gap of a plurality of nucleotides between the 5’ terminal nucleotide and 3’ terminal of the padlock probes with tiling probes of Mockler in the method of Hardenbol. The artisan would be motivated as Akhras suggests the use of CIPer methods in MIP methods. The teachings of Hardenbohl set forth one embodiment of the use of MIP or padlock probes. The artisan further would be motivated as Mockler teaches the probe tiling approach reduces bias (pg 2, col 1, para 4 to pg 2, col 2, para 1). The artisan would have a reasonable expectation of success as the artisan is merely increasing the number of nucleotides between the 3’ terminal nucleotide and 5’ terminal nucleotide of the probes of Mockler, which Akhras demonstrates were known and worked. Thus the combination of references suggests

all the limitations of claims and suggests the use of CIPer in place of the similar MIP methods.

Akhras, Nilsson, Hardenbohl, and Mockler do not specifically teach the use of probes at two or more concentrations.

However, Porecca teaches a method of amplifying human exons using MIPS. Porecca teaches, “It is both concerning and interesting that the resequencing data show skewing of base-calls at heterozygous positions away from the expected ratio of 0.5 (Fig. 4). This skewing might be expected if stochastic events (for example, a finite number of capture events during the multiplex capture reaction) are a primary source of bias. Given that the concentration of individual targeting oligos in the capture reaction is very low (B0.36 pM per species), it is likely that their hybridization to genomic DNA is inefficient. This problem might therefore be mitigated simply by increasing the concentration of reactants. If either the targeting oligos or genomic DNA can be defined as limiting, one could potentially hybridize with an excess of the complement, that is, to saturation, such that small differences in capture efficiency would be ‘normalized’ away.” Porecca further teaches, “After characterizing the efficiency of individual capture oligos in each reaction, a second iteration could be carried out, in which capture oligos performing similarly to one another are grouped together within the same oligo mixture (thereby maximizing uniformity within any single reaction).”

Further, Hardenbohl(PGPUB) teaches, “Genomic material is complex and thus individual sequences exist at relatively low concentrations in a mixture. As a result of this, at a given probe concentration there is a finite rate at which the probe sequences

will hybridize to the genomic templates. Probe concentrations can be adjusted to some extent to vary this rate, but as probe complexity is increased, for example, when highly multiplexed assays are used, such flexibility is greatly reduced" (003). Hardenbohl continues, "Multiplexing occurs at two levels in the invention. First, hybridization-based assays are designed to measure characteristics of one or more target polynucleotides, such as genomic fragments, at multiple loci. The number of loci measured in each hybridization-based assay can vary widely, and its upper limit depends on well-known factors, including the capacity of the readout device being employed, trade-offs selected between probe concentrations and reaction times, the genetic characteristic being measured (for example, trait association studies require very large numbers of measurements; genetic identification requires relative few measurements; testing for adverse drug reactions may require a medium number of measurements, e.g. several tens to hundreds), and the like. In one aspect, the number of loci analyzed in each hybridization-based assay is in the range of from a few tens, e.g. 10 to 20, to many thousands, e.g. fifty to a hundred thousand. In another aspect, the number of loci per hybridization-based assay is in the range of from 10 to 40,000; or it is in the range of from 100 to 30,000; or it is in the range of from 100 to 20,000. Second, multiplexing occurs from the combination of assay products from multiple hybridization-based assays for determining multiple signals on a single readout device. Usually, there is a one-to-one correspondence between the number of hybridization-based assay products combined in accordance with the invention and the number of different genomic samples being analyzed; however, the invention comprehends situations where

different numbers of samples from different individuals are analyzed by varying numbers of hybridization-based assays, the products of which are combined. The level of such multiplexing depends of the capacity of the readout device and the number of loci measured by each hybridization-based assay. In one aspect, the number of hybridization-based assays that may be multiplexed is simply the capacity of a readout device, e.g. the number of features on a microarray, divided by the number of loci being measured in the hybridization-based assays. For example, in one aspect, a 100 thousand-feature microarray can serve as a readout device for fifty hybridization based assays that each measure the zygosity of one thousand loci, when two features are required for each determination (e.g. homozygous in allele 1, homozygous in allele 2, or heterozygous in allele 1 and 2). As discussed more fully below, particular trade-offs between the use of microarray features, different colored fluorescent dyes, number of loci measured per hybridization-based assay, capacity of a readout device, and the like, are routine design choices for those of ordinary skill in the art."

Hardenbohl (PGPUB) continues, "Operation of one embodiment of the invention is illustrated in FIGS. 1A and 1B for a particular hybridization-based assay (one based on the template-driven ligation of two oligonucleotide components). Hybridization-based assays are carried out separately on a sample of DNA from genome G.sub.1 and a sample of DNA from genome G.sub.2. Probes p.sub.1 to p.sub.K (100) containing oligonucleotide tags t.sub.1 to t.sub.K, respectively, and probes p.sub.1 to p.sub.K (102) containing oligonucleotide tags t.sub.K+1 to t.sub.2K, respectively, are combined in separate reaction mixtures with genome G.sub.1 DNA and genome G.sub.2 DNA,

respectively, under conditions that permit specific hybridization of such probes to their respective DNA stands (104) and (106) containing target loci, L.sub.1 through L.sub.K ((108) to (110) for genome G.sub.1 and (112) to (114) for genome G.sub.2). After an incubation time depending on parameters well-known to those of ordinary skill, e.g. target complexity, probe concentration, temperature, and the like, discussed more fully below, probe-genome complexes form ((118) and (116), respectively) that include recognition structures for enzyme(s) of subsequent step(s)."

Finally, Browne demonstrates the use of dual inversion probes at different concentrations in figure 6.

As stated in the MPEP, 2144.05 II, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of Akhras, Nilsson, Hardenbohl, and Mockler to include at probes at different concentrations in a sample to optimize hybridization and assay conditions in a sample. The artisan would be motivated as Porecca, Hardenbohl(PGPUB), and Brown recognize that probe concentration is an optimizable variable in the speed and performance of hybridization assays including molecular inversion probe assays. Thus it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include additional probes at different concentrations so as to optimize efficiency of

hybridization as well as speed of hybridization in a sample. The artisan would have a reasonable expectation of success as the artisan is merely using known methods to optimize conditions.

Response to Arguments

The response traverses the rejection asserting the prior art does not teach, "wherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence." This argument has been thoroughly reviewed but is not considered persuasive as claim 1 has been amended to recite, "wherein the 5' region is complementary to a nucleic acid residue flanking 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." Thus a region a region encompasses a single nucleotide. Thus a subregion logically also encompasses a single nucleotide.

Further the claim has been amended to recite, "wherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence." First it is noted the subregion is a reference to the target nucleic acid and not the probe. Thus the wherein clause encompasses an intended outcome that is based on the target nucleic acid and not necessarily the probe. Alternatively the claims encompass any probe that has a subregion (nucleotide) that overlaps at least one other subregion (nucleotide) on another probe as a region is a nucleotide.

The response continues by asserting that figure 2D of Mockler does not render this limitation obvious. This argument has been thoroughly but is not considered

persuasive as the probes of Mockler encompass probes that have a sub-region (nucleotide) that entirely overlaps with a subregion (nucleotide) of another probe.

Double Patenting

2. 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.

3. Claims 1, 3-4 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 13934093 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because coextensive in scope.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Instant claim 1 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 setcomprising 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to a nucleic acid residue flanking 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; and wherein 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.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the “PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant’s specification.”

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable

interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

Claim 1 has been amended to recite, “wherein the 5' region is complementary to a nucleic acid residue flanking 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.” Thus a region a region encompasses a single nucleotide. Thus a subregion logically also encompasses a single nucleotide.

Further the claim has been amended to recite, “wherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence.” First it is noted the subregion is a reference to the target nucleic acid and not the probe. Thus the wherein clause encompasses an intended outcome that is based on the target nucleic acid and not necessarily the probe. Alternatively the claims encompass any probe that has a subregion (nucleotide) that overlaps at least one other subregion (nucleotide) on another probe as a region is a nucleotide.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) “adapted to” or “adapted for” clauses;

(B) “wherein” clauses; and

(C) “whereby” clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Claim 1 of '093 requires A method of analyzing a human nucleic acid for carrier screening, the method comprising: providing a sample from a human, the sample comprising human nucleic acid comprising-a target nucleic acid; introducing a plurality of molecular inversion probes to the sample, each molecular inversion probe comprising a 5' region comprising a 5' terminal nucleotide; a 3' region comprising a 3' terminal nucleotide, and a central region flanked by the 5' region and the 3' region; wherein the 5' region and the 3' region of each molecular inversion probe are complementary to nucleic acid residues flanking a same strand of one of a plurality of sub-regions of ~~one~~ the target nucleic acid; wherein the plurality of molecular inversion probes are configured to tile across the target nucleic acid with each sub-region overlapping with at least one other sub- region on the target nucleic acid; and wherein each molecular

inversion probe consists of one of the nucleotide sequences selected from the group consisting of SEQ ID NO: 185 through SEQ ID NO: 3,254;hybridizing at least a portion of the molecular inversion probes to a plurality of the sub- regions of the human nucleic acid, wherein the plurality of sub-regions of the human nucleic acid are from a combination of genes comprising ATP-binding cassette, sub-family C (CFTR/MRP),Serial No.: 13/934,093member 8 (ABCC8), aspartoacylase (ASPA), branched chain keto acid dehydrogenase E1, alpha polypeptide (BCKDHA), branched chain keto acid dehydrogenase E1, beta polypeptide (BCKDHB), Bloom Syndrome, RecQ Helicase-Like (BLM), cystic fibrosis transmembrane conductance regulator (CFTR), clarin 1 (CLRN1), dihydrolipoamide dehydrogenase (DLD), Fanconi anemia, complementation group C (FANCC), glucose-6-phosphatase, catalytic subunit (G6PC), hexosaminidase A alpha polypeptide (HEXA), inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein (IKBKAP), mucolipin 1 (MCOLN1), protocadherin-related 15 (PCDH15), and sphingomyelin phosphodiesterase 1, acid lysosomal (SMPD1);converting the hybridized probes into covalently-closed circularized probes;isolating a plurality of circularized probes, each circularized probe containing a captured sub-region comprising a copy of one of the sub-regions; amplifying the circularized probes;sequencing the captured sub-regions; and analyzing the sequence to detect a mutation, thereby determining whether the human is a carrier of a disease.

Thus the claims render the instant claims obvious as they are a species of the instant claims.

4. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No. 8,778,609. This is a statutory double patenting rejection.

Instant claim 1 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 setcomprising 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to a nucleic acid residue flanking 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; and wherein 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.

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in

an infringement suit. Rather, the “PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant’s specification.”

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

Claim 1 has been amended to recite, “wherein the 5' region is complementary to a nucleic acid residue flanking 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.” Thus a region a region encompasses a single nucleotide. Thus a subregion logically also encompasses a single nucleotide.

Further the claim has been amended to recite, “wherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence.” First it is noted the subregion is a reference to the target nucleic acid and not the probe. Thus the wherein clause encompasses an intended outcome that is based on the target nucleic acid and not necessarily the probe. Alternatively the claims encompass any probe that has a subregion (nucleotide) that overlaps at least one other subregion (nucleotide) on another probe as a region is a nucleotide.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) “adapted to” or “adapted for” clauses;

(B) “wherein” clauses; and

(C) “whereby” clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a “wherein” clause limited a process claim where the clause gave “meaning and purpose to the manipulative steps”). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a “‘whereby’ clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.” Id. However, the court noted (quoting Minton v. Nat’l Ass’n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a “‘whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.’” Id.

Claim 1 of 609 requires, “1. A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein

immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template."

Claim 2 of 609 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 2 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

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

Electronic Acknowledgement Receipt	
EFS ID:	30390076
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 29258/20
Receipt Date:	18-SEP-2017
Filing Date:	13-MAR-2012
Time Stamp:	14:29:42
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$700
RAM confirmation Number	091917INTEFSW00000792500369
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		29258_20_OA_Response.pdf	122769 adf0c44f2df84f68b00805017f41b84d32fb2bf3	yes	12

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	8
Applicant Arguments/Remarks Made in an Amendment	9	12

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30722 27387bf0221eebb6ab535750f434c5c22f91c1e3	no	2

Warnings:

Information:

Total Files Size (in bytes):	153491

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-002/01US 29258/20
Serial No.: 13/266,862

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	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 the non-final office action mailed March 16, 2017, from the United States Patent and Trademark Office. Applicant petitions for a 3-month extension of time to bring the response date up to and including Monday, September 18, 2017. Applicant pays the extension of time fee, and authorizes the Commissioner to charge any other required fee to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 9.

Amendment to the claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently Amended) 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to [[a]] nucleic acid residues flanking 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 residues flanking a 5' end of the ~~subregion~~ target nucleic acid; ~~wherein each subregion is different and overlaps with at least one other subregion; and wherein at least one subregion entirely overlaps at least one other subregion and captures additional flanking sequence;~~ and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the entire target nucleic acid;

isolating [[a]] the plurality of circularized probes ~~having nucleic acid sequences of different subregions~~; and

analyzing the ~~isolated subregions~~ target nucleic acid.

2. (Canceled)

Petitioner Illumina, Inc., EX1002, p. 1189

3. (Original) 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. (Original) 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.

5-11. (Canceled)

12. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 12, 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. (Withdrawn) The method of claim 12, wherein the threshold number for a specific target nucleic acid sequence is selected based on a desired statistical confidence for the genotype.

16. (Withdrawn) The method of claim 12, further comprising determining a statistical confidence for the genotype based on the number of unique combinations of target nucleic acid and differentiator tag sequences.

17-19. (Canceled)

20. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 20, wherein the capture efficiency is lower than the reference capture efficiency.

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

24. (Withdrawn) The method of claim 20, wherein the capture efficiency is higher than the reference capture efficiency.

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

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

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

28. (Withdrawn) The method of claim 20, wherein a sub-target nucleic acid is captured from the target nucleic acid using a molecular inversion probe.

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

31-32. (Canceled)

33. (Withdrawn) The method of claim 29, wherein the first and second targeting arms have the same length.

34-35. (Canceled)

36. (Withdrawn) The method of claim 29, wherein the hybridization Tms of the first and second targeting arms are identical.

37. (Withdrawn) The method of claim 28, wherein the sub-target nucleic acid contains a nucleic acid repeat.

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

39. (Canceled)

40. (Withdrawn) 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. (Withdrawn) The method of claim 29, 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.

42. (Withdrawn) The method of claim 29, 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.

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43. (Withdrawn) The method of claim 29, 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. (Withdrawn) The method of claim 20, wherein a plurality of different target nucleic acids are analyzed in a biological sample.

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

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

48-49. (Canceled)

50. (Withdrawn) The method of claim 20, wherein the capture efficiency is evaluated by determining an amount of target nucleic acid that is captured.

51. (Withdrawn) 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.

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

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53. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 20, 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.

57-67. (Canceled)

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Remarks

Claims 1, 3, and 4 are pending in the application. Claim 1 is amended to clarify the nature of the overlapping probes. Support for the amendment is found in the published application at paragraphs [0027]-[0028] and [0121]-[0127]. No new matter is added.

Rejection under 35 U.S.C. §112, first paragraph

The Office Action rejects claims 1, 3, and 4 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement. In particular, the Office Action alleges that the specification does not support "wherein the 5' region is complementary to a nucleic acid residue flanking 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" because a 5' region and a 3' region being complementary to a single nucleotide. The claim has been amended to recite "nucleic acid residues" and therefore Applicant believes the rejection is overcome.

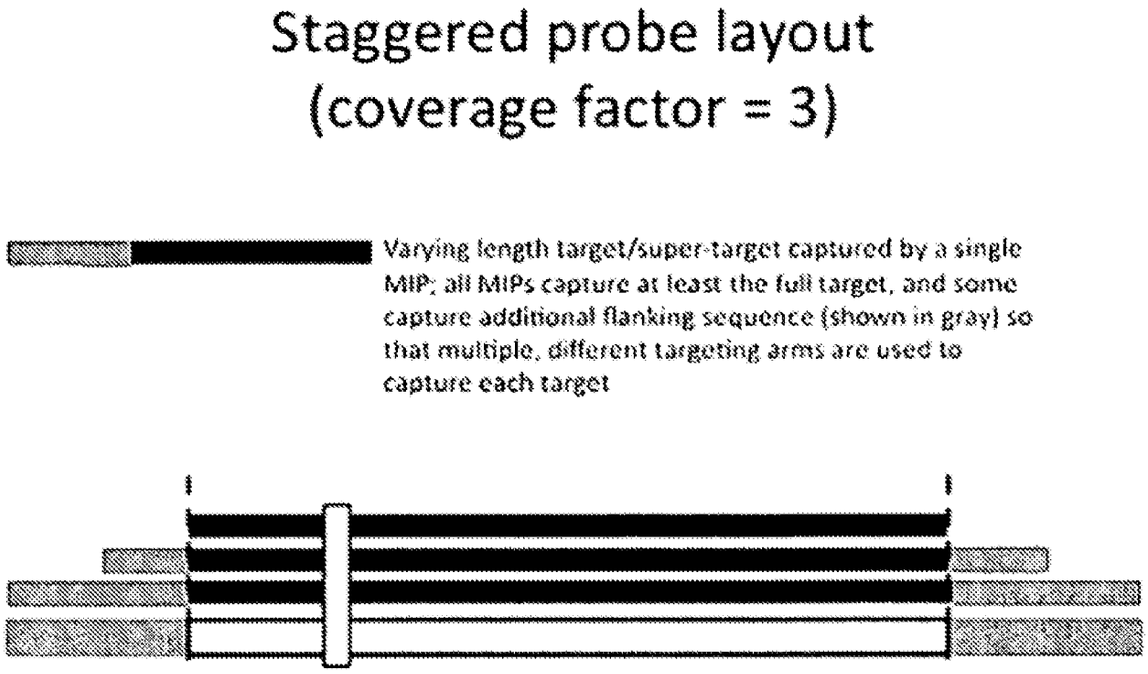
Rejections under 35 U.S.C. §103

The Office Action maintains the rejections of claims 1, 3, and 4 under 35 U.S.C. §103(a) over the combination of Akhras (PLOS one, 2007, 2(9):e915), Nilsson (Trends in Biotechnology, 2006, 24:83-88), Hardenbol (Nature Biotechnology, 2003, 21:673-78), Mockler (Genomics, 2005, 85:1-15), Porreca (Nature Methods, 2007, 4:931-36), Hardenbol (2006/0019304), and Browne (2006/0246500). Applicants submit that the present claims are not made obvious by any combination of those references.

The office action indicates on page 17 that the rejection relies on an interpretation of the claims that includes a subregion being a single nucleotide. The rejection also relies on an interpretation of "the subregion entirely overlaps at least one other subregion and captures additional flanking sequence" to encompass the two subregions merely being the same nucleotide. While Applicant disagrees with this interpretation, in order to advance prosecution

the claims have been amended to clarify the nature of the probes, and the claims no longer recite subregions. Additionally, the claims make clear that the captured sequence is not as an intended outcome but rather is a feature of the circularized probes. Applicant submits that the present claims are therefore not made obvious by the prior art.

The claims require molecular inversion probes complimentary to nucleic acid residues flanking a target nucleic acid, wherein the complimentary regions do not overlap with each other. The probes are circularized to capture the target nucleic acid, and the resulting circularized probes contain the entire target nucleic acid. This "staggered probe layout" embodiment is shown clearly in FIG. 2 of the application, reproduced below.

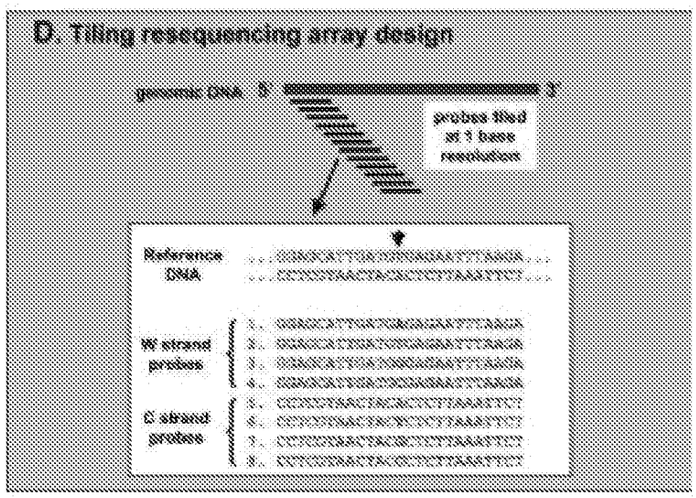


As explained in the specification at page 35, lines 3-15, the set of molecular inversion probes can be designed to "stagger" the exact positions of the hybridization regions (i.e., the 5' region and the 3' region) flanking the target. That allows the MIPs to capture the full target with multiple probes having different targeting arms. Since the MIPs in the set are different, this variability in targeting arms solves problems associated with inefficient probe hybridization. *See id., page 34, lines 30-32.*

None of the prior art references discloses or suggests a set of molecular inversion probes having different targeting arms and are configured to be converted to circularized probes that contain the entire target nucleic acid.

Mockler is the only reference that the Office Action alleges shows that element. However, Applicants disagree with the interpretation of Mockler.

Mockler reports various probe tiling strategies in FIGS. 2A-D, but none of those tiling strategies include the staggered probe layout that could produce the presently claimed circularized entities. The embodiment in Mockler that the Office Action points to is that of FIG. 2D, reproduced below.



As shown in FIG. 2D, the probes are tiled at 1-base resolution. The probes are not designed to capture the entire target nucleic acid and the captured sequences do not overlap in the manner presently claimed. Accordingly, Mockler fails to disclose or suggest the present claim element of converting the hybridized probes into a plurality of closed circularized probes, each comprising the entire target nucleic acid.

Since none of the references shows that element, no combination of the cited art makes the present claims obvious. Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103(a).

Double Patenting

The claims are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending application number 13/934,093. Since the rejection is provisional, Applicant requests that it be held in abeyance.

Summary

On the basis of the foregoing reasons, Applicants respectfully submit that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative.

Dated: September 18, 2017

Respectfully submitted,
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Petitioner Illumina, Inc., EX1002, p. 1199

Electronic Patent Application Fee Transmittal	
Application Number:	13266862
Filing Date:	13-Mar-2012
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-002/01US 29258/20
Filed as Small Entity	
Filing Fees for U.S. National Stage under 35 USC 371	

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 $0 paid	2253	1	700	700
Miscellaneous:				
		Total in USD ($)		**700**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	GSGE-002/01US 29258/20	6082

21710 7590 11/09/2017

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/09/2017	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. 13/266,862	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 *9/18/2017*.

☐ 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) *1,3,4,12-16,20-30,33,36-38,40-47 and 50-56* is/are pending in the application.

5a) Of the above claim(s) *12-16,20-30,33,36-38,40-47 and 50-56* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3 and 4* 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 *4/8/2013* 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., EX1002, p. 1203

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

2. 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 9/18/2017.

Claims 1, 3-4, 12-16, 20-30, 33, 36-38, 40-47 and 50-56 are pending.

Claims 2, 5-11, 17-19, 31-32, 34-35, 39-38, 48-49 and 57-67 have been canceled.

Claims 12-16, 20-30, 33, 36-38, 40-47 and 50-56 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention , there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/3/2012.

Claims 1, 3-4 are being examined.

Claim 1 has been amended. To broaden the claim by deleting, “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.” Thus the amendment allows for a broader interpretation of the claim and thus new art to be applied.

The previous art rejections have been amended in view of the amendment to the claims.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Specification

3. 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, " the entire target nucleic acid." The specification does not provide antecedent basis for "the entire target nucleic acid."

Response to Arguments

This is a new ground of objection necessitated by amendment.

Claim Rejections - 35 USC § 112

4. 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.

5. Claims 1, 3-4 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 1 recites the limitation "the entire target nucleic acid" in the converting step. There is insufficient antecedent basis for this limitation in the claim as the claim does not previously recite, “entire target nucleic acid.” The specification states, “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).”The specification and claim do not provide a limiting definition of “entire target nucleic acid” or “target nucleic acid.” Thus it is unclear what is required of "the entire target nucleic acid" as the claim and specification do not clearly indicate what is required. It is unclear if the entire target nucleic acid is the sequence between the 3’ region and the 3'region or if it requires something more.

Claims 3-4 are rejected as they depend from claim 1.

Response to Arguments

This is a new ground of objection necessitated by amendment.

Claim Rejections - 35 USC § 102

6. 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.

7. 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.

8. Claim(s) 1 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Akhras et al (PLOS one (2007) volume 2 (9) e915) (IDS 3/28/2013).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the “PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant’s specification.”

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, “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).” Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

Akhras teaches, “The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay [17], which includes: i) probe hybridization, single “G” base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by relinearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target (Figure 1B). The 39end of the probe, which we call the Extension Site (ES), primes for polymerization, while the 59end serves as point of ligation and is referred to as the Anchor Site (AS) (Figure 1). With

all four dNTPs present, the polymerase is capable of extending past the intended point of ligation, generating a false negative. To address this problem, probes were designed to have an annealing temperature of approximately 5 degrees higher for the AS than that of the ES. The AS therefore blocks DNA extension when using a polymerase deficient in strand displacement at an appropriate intermediate temperature (50uC). For enhanced sensitivity and specificity a vast variety of probe concentrations and thermoprofiles were explored. Probes used in the 10–100 fmol concentration range yielded the strongest signal. Higher cycle numbers and shorter annealing times created a more efficient thermoprofile. The CIPer method successfully genotyped 1 pg of plasmid DNA in the presence of 200 ng non-reacting human genomic DNA, without generating any false positives (Figure S1). Assay optimizations were based on genotyping of HPV plasmid 56, validated by either SYBR GREEN assay or agarose gel electrophoresis, followed by Pyrosequencing verification (see Results, The Conserved Sequence Primer Connector Inversion Probe (CSP-CIPer)).”

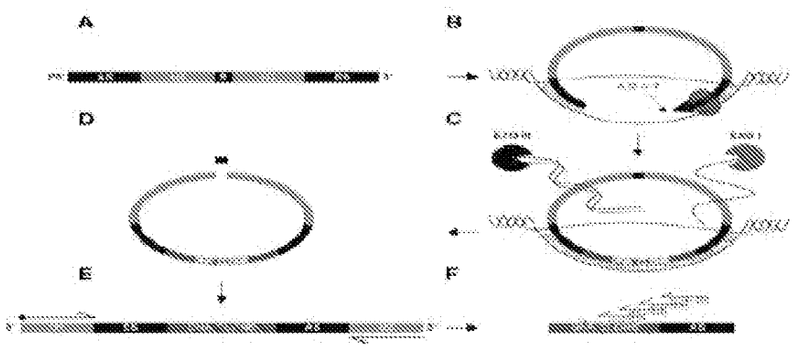


Figure 1. Schematic overview of Connector Inversion Probe (CIPer) technology. A) Synthetic oligonucleotide containing regions *A5 and B5* (anchor site and extension site) approximately 20 base pair fragments homologous to regions flanking target of interest. B) *R*: restriction site for probe linearization, B) *U1 and U2*: universal primer regions for inverted probe amplification. B) Target rescue through complete gap filling by a DNA polymerase and ligation-based probe circularization. C) Circular DNA enrichment through degradation of linear DNA by enzymes Exonuclease I and III, which are deactivated prior to the next step. D) Probe linearization by restriction site cleavage. E) Inverted probes are amplified with universal primers; one is biotinylated for subsequent amplicon validation. F) Amplicon validation using multiple sequencing primers
doi:10.1371/journal.pone.0008918.g001

Thus Akhras teaches providing a sample comprising a target nucleic acid (DNA clone), contacting the sample with a plurality of probes that flank the target nucleic acid with flanking 3' and 5' ends, converting the hybridized probe to a plurality of circularized probes comprising the entire target sequences, isolating the probes and sequence the target nucleic acids.

Response to Arguments

This is a new ground of rejection necessitated by amendment.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 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 of this title, 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. Claims 1, 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akhras et al (PLOS one (2007) volume 2 (9) e915) (IDS 3/28/2013), Nilsson et al (Trends in Biotechnology (2006) volume 24, pages 83-88), Hardenbohl et al (Nature Biotechnology(2003) volume 21, pages 673-678), Mockler et al (Genomics (2005) volume 85, pages 1-15),.

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the

broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

Akhras teaches, "The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay [17], which includes: i) probe hybridization, single "G" base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by relinearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an

extensive gap formed by the probe and target (Figure 1B). The 39end of the probe, which we call the Extension Site (ES), primes for polymerization, while the 59end serves as point of ligation and is referred to as the Anchor Site (AS) (Figure 1). With all four dNTPs present, the polymerase is capable of extending past the intended point of ligation, generating a false negative. To address this problem, probes were designed to have an annealing temperature of approximately 5 degrees higher for the AS than that of the ES. The AS therefore blocks DNA extension when using a polymerase deficient in strand displacement at an appropriate intermediate temperature (50uC). For enhanced sensitivity and specificity a vast variety of probe concentrations and thermoprofiles were explored. Probes used in the 10–100 fmol concentration range yielded the strongest signal. Higher cycle numbers and shorter annealing times created a more efficient thermoprofile. The CIPer method successfully genotyped 1 pg of plasmid DNA in the presence of 200 ng non-reacting human genomic DNA, without generating any false positives (Figure S1). Assay optimizations were based on genotyping of HPV plasmid 56, validated by either SYBR GREEN assay or agarose gel electrophoresis, followed by Pyrosequencing verification (see Results, The Conserved Sequence Primer Connector Inversion Probe (CSP-CIPer)).”

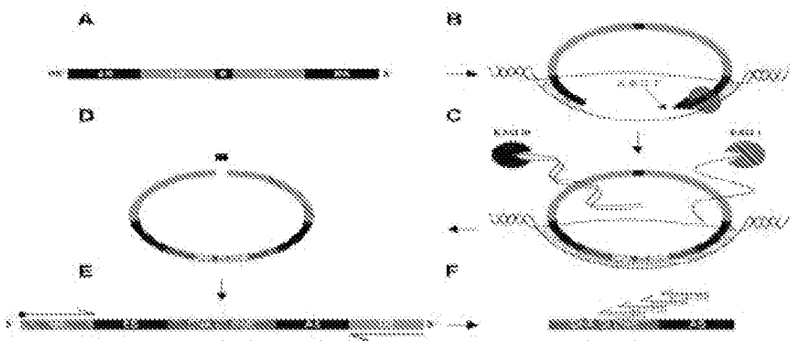


Figure 1. Schematic overview of Connector Inversion Probe (CIPer) technology. A) Synthetic oligonucleotide containing regions i) AS and ES (anchor site and extension site); approximately 30 base pair fragments homologous to regions flanking target of interest, ii) R restriction site for probe linearization, iii) U1 and U2: universal primer regions for inverted probe amplification. B) Target rescue through complete gap filling by a DNA polymerase and ligation-based probe circularization. C) Circular DNA enrichment through degradation of linear DNA by enzymes Exonuclease I and III, which are deactivated prior to the next step. D) Probe linearization by restriction site cleavage. E) Inverted probes are amplified with universal primers: one is biotinylated for subsequent amplicon validation. F) Amplicon validation using multiple sequencing primers.
doi:10.1371/journal.pone.0000913.g001

Thus Akhras teaches providing a sample comprising a target nucleic acid (DNA clone), contacting the sample with a plurality of probes that flank the target nucleic acid with flanking 3’ and 5’ ends, converting the hybridized probe to a plurality of circularized probes comprising the entire target sequences, isolating the probes and sequence the target nucleic acids.

Arkhas does not teach having probes at the 5’ and 3’ end having different sequences.

Mockler, teaches each subregion overlaps with at least one other subregion (Fig. 2a).

With regards to claim 4, Mockler teaches 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 (Fig. 2a-H1 and H2 unique to each probe).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the CIPer or selector probes taught by

Akhras with a gap of 20 nucleotides tiling probes of Mockler with a target nucleic acid of 2-4 nucleotides, resulting in multiple probes with different 3' and 5' flanking arms (differe by one nucleotide) and encompass the whole target sequence. The artisan would be motivated as Akhras suggests the use of CIPer methods in MIP methodsThe artisan further would be motivated as Mockler teaches the probe tiling approach reduces bias (pg 2, col 1, para 4 to pg 2, col 2, para 1). The artisan would have a reasonable expectation of success as the artisan is merely increasing the number of nucleotides between the 3' terminal nucleotide and 5' terminal nucleotide of the probes of Mockler, which Akhras demonstrates were known and worked. Thus the combination of references suggests all the limitations of claims and suggests the use of CIPer in place of the similar MIP methods. The artisan would have a reasonable expectation of success as the artisan is merely combining known methods.

With regards to claim 3 Mockler teaches probes in figures 2 a and 2b which are non-overlapping covering the entire genomic sequence.

The specification and claims do not teach or recite a limiting definition of "the entire target nucleic acid." The broadest reasonable interpretation of entire nucleic acids is the sequence that is hybridized between the 3' and 5' region of each probe.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the CIPer or selector probes taught by Akhras with a gap of 20 nucleotides tiling probes of Mockler with a target nucleic acid of 2-4 nucleotides, resulting in multiple probes with different non-overlapping 3' and 5' flanking arms and encompass the whole target sequence. The artisan would be

motivated as Akhras suggests the use of CIPer methods in MIP methods. The teachings of Hardenbohl set forth one embodiment of the use of MIP or padlock probes. The artisan further would be motivated as Mockler teaches the probe tiling approach reduces bias (pg 2, col 1, para 4 to pg 2, col 2, para 1). The artisan would have a reasonable expectation of success as the artisan is merely increasing the number of nucleotides between the 3' terminal nucleotide and 5' terminal nucleotide of the probes of Mockler, which Akhras demonstrates were known and worked. Thus the combination of references suggests all the limitations of claims and suggests the use of CIPer in place of the similar MIP methods. The artisan would have a reasonable expectation of success as the artisan is merely combining known methods.

Response to Arguments

The response traverses the rejection asserting, "The office action indicates on page 17 that the rejection relies on an interpretation of the claims that includes a subregion being a single nucleotide. The rejection also relies on an interpretation of "the subregion entirely overlaps at least one other subregion and captures additional flanking sequence" to encompass the two subregions merely being the same nucleotide. While Applicant disagrees with this interpretation, in order to advance prosecution." This argument has been thoroughly reviewed but is not considered persuasive as the rejection has been amended in view of this amendment.

The response continues by providing arguments with respect to complimentary regions not overlapping. This argument has been thoroughly reviewed but is not considered persuasive as figure 2 A and 2B of Mockler teach non-overlaping probes. .

The response traverses the rejection by asserting, " None of the prior art references discloses or suggests a set of molecular inversion probes having different targeting arms and are configured to be converted to circularized probes that contain the entire target nucleic acid." This argument has been thoroughly reviewed but is not considered persuasive as the claims and specification do not provide any limiting definition of a target nucleic acid and the rejection indicates the target nucleic acid could be 2-4 nucleotides. Thus this argument is not persuasive.

The response continues by providing arguments that Mockler does not teach the staggered probes of the instant specification as apparently encompassed by claim 3. This argument is not persuasive the “entire target nucleic acid" is indefinite and in view of the indefiniteness figures 2 A and B teach probes that are not overlapping.

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 1, 3-4 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 13934093

(reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because coextensive in scope.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Instant claim 1 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 setcomprising 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to a nucleic acid residue flanking 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; and wherein 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.

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the “PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant’s specification.”

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, “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).” Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language,

although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) “adapted to” or “adapted for” clauses;

(B) “wherein” clauses; and

(C) “whereby” clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a “wherein” clause limited a process claim where the clause gave “meaning and purpose to the manipulative steps”). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a “‘whereby’ clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.” Id. However, the court noted (quoting Minton v. Nat’l Ass’n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a “‘whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.’” Id.

Claim 1 of ‘093 requires A method of analyzing a human nucleic acid for carrier screening, the method comprising: providing a sample from a human, the sample comprising human nucleic acid comprising-a target nucleic acid; introducing a plurality of molecular inversion probes to the sample, each molecular inversion probe comprising a 5' region comprising a 5' terminal nucleotide; a 3' region comprising a 3' terminal nucleotide, and a central region flanked by the 5' region and the 3' region; wherein the 5'

region and the 3' region of each molecular inversion probe are complementary to nucleic acid residues flanking a same strand of one of a plurality of sub-regions of ~~one~~ the target nucleic acid; wherein the plurality of molecular inversion probes are configured to tile across the target nucleic acid with each sub-region overlapping with at least one other sub- region on the target nucleic acid; and wherein each molecular inversion probe consists of one of the nucleotide sequences selected from the group consisting of SEQ ID NO: 185 through SEQ ID NO: 3,254;hybridizing at least a portion of the molecular inversion probes to a plurality of the sub- regions of the human nucleic acid, wherein the plurality of sub-regions of the human nucleic acid are from a combination of genes comprising ATP-binding cassette, sub-family C (CFTR/MRP),Serial No.: 13/934,093member 8 (ABCC8), aspartoacylase (ASPA), branched chain keto acid dehydrogenase E1, alpha polypeptide (BCKDHA), branched chain keto acid dehydrogenase E1, beta polypeptide (BCKDHB), Bloom Syndrome, RecQ Helicase-Like (BLM), cystic fibrosis transmembrane conductance regulator (CFTR), clarin 1 (CLRN1), dihydrolipoamide dehydrogenase (DLD), Fanconi anemia, complementation group C (FANCC), glucose-6-phosphatase, catalytic subunit (G6PC), hexosaminidase A alpha polypeptide (HEXA), inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein (IKBKAP), mucolipin 1 (MCOLN1), protocadherin-related 15 (PCDH15), and sphingomyelin phosphodiesterase 1, acid lysosomal (SMPD1);converting the hybridized probes into covalently-closed circularized probes;isolating a plurality of circularized probes, each circularized probe containing a captured sub-region comprising a copy of one of the sub-regions;

amplifying the circularized probes;sequencing the captured sub-regions; and analyzing the sequence to detect a mutation, thereby determining whether the human is a carrier of a disease.

The dependent claims are merely obvious variant of the independent claims and obvious over the art of record.

Thus the claims render the instant claims obvious as they are a species of the instant claims.

Response to Arguments

The response request the provisional rejection be held in abeyance.

13. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No. 8,778,609. This is a statutory double patenting rejection.

Instant claim 1 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 setcomprising 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to a nucleic acid residue flanking 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; and wherein

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.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the “PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant’s specification.”

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, “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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a

method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Claim 1 of 609 requires, "1. A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template."

Claim 2 of 609 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 2 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a

reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response provides no arguments to the instant rejection and thus appears to acquiesce on the rejection.

Summary

No claims are allowed.

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

Electronic Acknowledgement Receipt	
EFS ID:	32561876
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 29258/20
Receipt Date:	09-MAY-2018
Filing Date:	13-MAR-2012
Time Stamp:	12:14:54
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1650
RAM confirmation Number	050918INTEFSW00010208500369
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-002-01US-Response-to-FOA.pdf	125043 7f65323c995e04050698ea7c1cf2c91af4e8cedb	yes	13

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment Submitted/Entered with Filing of CPA/RCE	1	1
	Claims	2	8
	Applicant Arguments/Remarks Made in an Amendment	9	13

Warnings:					
Information:					
2	Request for Continued Examination (RCE)	GSGE-002-01US-RCE.pdf	1362383 ae246f0f465880f6be95e124aad70e1c729a7c53	no	3
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32609 d73a910a8eec6c967225201e04ff3ff6df13868a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1520035		

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:	Porreca et al.	ART UNIT:	1634
SERIAL NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	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 REQUEST FOR CONTINUED EXAMINATION

This paper is in response to the final office action mailed November 9, 2017, from the United States Patent and Trademark Office. Applicant submits herewith a Request for Continued Examination (RCE) and petitions for a 3-month extension of time to bring the response date up to and including May 9, 2018. Applicant pays the RCE fee and the extension of time fee, and authorizes the Commissioner to charge any other required fee to Deposit Account No. 50-0369.

Amendments to the claims begin on page 2.

Remarks begin on page 9.

Amendment to the claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently Amended) 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe; and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the ~~entire~~ target nucleic acid;

isolating the plurality of circularized probes; and

analyzing the target nucleic acid.

2. (Canceled)

3. (Original) 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.

Petitioner Illumina, Inc., EX1002, p. 1232

4. (Original) 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.

5-11. (Canceled)

12. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 12, 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. (Withdrawn) The method of claim 12, wherein the threshold number for a specific target nucleic acid sequence is selected based on a desired statistical confidence for the genotype.

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16. (Withdrawn) The method of claim 12, further comprising determining a statistical confidence for the genotype based on the number of unique combinations of target nucleic acid and differentiator tag sequences.

17-19. (Canceled)

20. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 20, wherein the capture efficiency is lower than the reference capture efficiency.

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

24. (Withdrawn) The method of claim 20, wherein the capture efficiency is higher than the reference capture efficiency.

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

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

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

28. (Withdrawn) The method of claim 20, wherein a sub-target nucleic acid is captured from the target nucleic acid using a molecular inversion probe.

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

31-32. (Canceled)

33. (Withdrawn) The method of claim 29, wherein the first and second targeting arms have the same length.

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34-35. (Canceled)

36. (Withdrawn) The method of claim 29, wherein the hybridization Tms of the first and second targeting arms are identical.

37. (Withdrawn) The method of claim 28, wherein the sub-target nucleic acid contains a nucleic acid repeat.

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

39. (Canceled)

40. (Withdrawn) 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. (Withdrawn) The method of claim 29, 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.

42. (Withdrawn) The method of claim 29, 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. (Withdrawn) The method of claim 29, 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.

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44. (Withdrawn) The method of claim 20, wherein a plurality of different target nucleic acids are analyzed in a biological sample.

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

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

48-49. (Canceled)

50. (Withdrawn) The method of claim 20, wherein the capture efficiency is evaluated by determining an amount of target nucleic acid that is captured.

51. (Withdrawn) 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.

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

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

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54. (Withdrawn) 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. (Withdrawn) 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. (Withdrawn) The method of claim 20, 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.

57-67. (Canceled)

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Remarks

Claims 1, 3, and 4 are pending in the application. Claim 1 is amended to clarify the nature of the overlapping probes. Support for the amendment is found in the published application at paragraphs [0027]-[0028] and [0121]-[0127]. No new matter is added.

Rejection under 35 U.S.C. §112, second paragraph

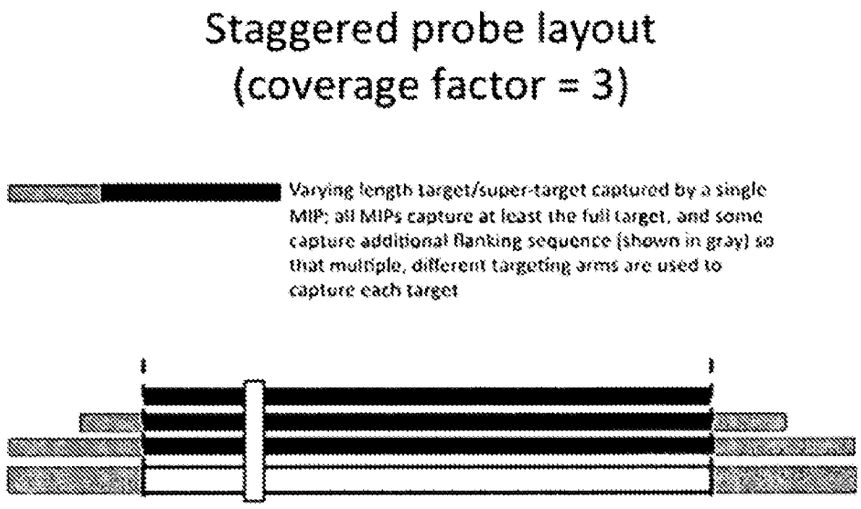
The Office Action rejects claims 1, 3, and 4 under 35 U.S.C. §112, second paragraph, for being indefinite for lacking antecedent basis for the term "the entire target nucleic acid." Claim 1 is amended to remove that term, rendering the rejection moot.

Rejections under 35 U.S.C. §102

The office action states that claim 1 is rejected under 35 U.S.C. §102(a) over Akhras (PLOS one, 2007, 2(9):e915). Applicant disagrees.

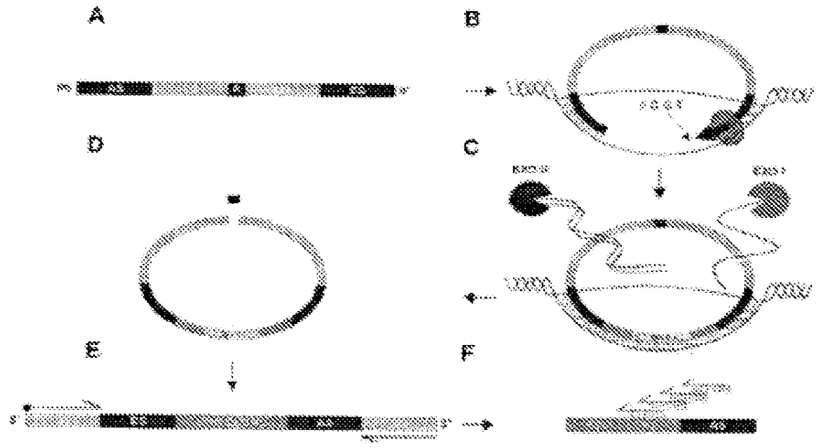
In order to anticipate a claim, the Office requires that a single prior art reference discloses each and every element of the claim. MPEP 2131. Akhras does not disclose probes whose 5' region and 3' region do not overlap with the 5' region and 3' region of another probe in the probe set, which gives the presently claimed invention the staggered probe layout described below.

The claims require molecular inversion probes that are complimentary to nucleic acid residues flanking a target nucleic acid, wherein the complimentary regions of different probes do not overlap with each other. Each probe captures the target nucleic acid, and the resulting circularized probes contain the entire target nucleic acid. This "staggered probe layout" embodiment is shown clearly in FIG. 2 of the application, reproduced below.



As explained in the specification at page 35, lines 3-15, the set of molecular inversion probes can be designed to "stagger" the exact positions of the hybridization regions (i.e., the 5' region and the 3' region) flanking the target. That allows the MIPs to capture the full target with multiple probes having different targeting arms. Since the MIPs in the set are different, this variability in targeting arms solves problems associated with inefficient probe hybridization. *See id., page 34, lines 30-32.*

Akhras does not disclose a staggered probe layout as presently claimed. Akhras discloses an oligonucleotide probe containing 3' and 5' regions that bind to regions flanking a target, and then circularize to enrich the target DNA. This is shown in FIG. 1, reproduced below.



Although Akhras shows probes with binding regions that flank and capture a target

sequence, Akhras fails to disclose probes that have complimentary regions that do not overlap with the complimentary regions of other probes, to achieve a staggered probe layout for capturing the entire target.

Since Akhras does not disclose at least one element of the independent claim, Applicant submits that the claims are not anticipated by that reference. Applicant requests that the 35 U.S.C. §102 rejection be withdrawn.

Rejections under 35 U.S.C. §103

The Office Action states that claims 1 and 4 are rejected under 35 U.S.C. §103(a) over the combination of Akhras (PLOS one, 2007, 2(9):e915), Nilsson (Trends in Biotechnology, 2006, 24:83-88), Hardenbohl (Nature Biotechnology, 2003, 21:673-78), and Mockler (Genomics, 2005, 85:1-15). Applicant submits that the present claims are not made obvious by that combination of references.

None of the prior art references discloses or suggests a set of molecular inversion probes having different targeting arms that do not overlap, each probe configured to be converted to circularized probes that contain the target nucleic acid. In fact none of those references appreciates the problem of bias in a capture reaction, which the present claims solve. Accordingly there would be no motivation to modify the references to include the missing feature.

As explained above, Akhras does not disclose a probe set where complimentary regions of different probes do not overlap with each other. None of Nilsson, Hardenbohl, or Mockler make up for what Akhras lacks.

Nilsson and Hardenbohl merely disclose padlock probes or molecular inversion probes but do not suggest the presently claimed staggering strategy. Hardenbohl presents a probe layout that involves padlock probes with targeting arms that hybridize with a separation of a single nucleotide. *See Hardenbohl, page 674, FIG. 2.* But Hardenbohl does not disclose a probe set of molecular inversion probes that are complimentary to nucleic acid residues flanking a target

nucleic acid, wherein the complimentary regions do not overlap with each other to form a staggered probe layout, as presently claimed.

Mockler reports various probe layouts in FIGS. 2A-D, but is silent regarding the staggered probe layout that could produce the presently claimed circularized entities. Mockler reports tiling a set of probes across a target region such that no probe captures the entire region on its own. *See Mockler, FIG. 2D*. The probes in Mockler are not designed to capture the entire target nucleic acid and the captured sequences do not overlap in the manner presently claimed.

Accordingly, no combination of Akhras, Nilsson, Hardenbohl, and Mockler teach the overlapping probe layout of the present invention. Since none of the references shows that element, no combination of the cited art makes the present claims obvious. Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §103.

Double Patenting

The claims are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending application number 13/934,093. Since the rejection is provisional, Applicant requests that it be held in abeyance.

Summary

On the basis of the foregoing reasons, Applicants respectfully submit that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicants' representative.

Dated: May 9, 2018

Respectfully submitted,
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63023819 v1

Petitioner Illumina, Inc., EX1002, p. 1243

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	13/266,862	Filing Date	2012-03-13	Docket Number (if applicable)	GSGE-002/01US 29258/20	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)	2018-05-09
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 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:	13266862
Filing Date:	13-Mar-2012
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-002/01US 29258/20
Filed as Small Entity	
Filing Fees for U.S. National Stage under 35 USC 371	

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 $0 paid	2253	1	700	700
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	950	950
		Total in USD ($)		**1650**

Electronic Acknowledgement Receipt

EFS ID:	33141737
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 29258/20
Receipt Date:	11-JUL-2018
Filing Date:	13-MAR-2012
Time Stamp:	19:10:24
Application Type:	U.S. National Stage under 35 USC 371

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	Rodriguez-2010-BullAmSoc.pdf	242429 7aaee0f04ee80effba35479ca1e26bcdc314c968	no	11

Warnings:

Information:					
2	Non Patent Literature	Schiffman-2009-CancGenCyt.pdf	870335 7fd707d04dead01854a5f88b62b3332bfbff53e6	no	10
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3	Non Patent Literature	Schneeberger-2011-PNAS.pdf	208006 d570cc89e26de029d5434f7e12284f8123b811de	no	6
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4	Non Patent Literature	Schouten.pdf	1112381 2f3699994d4cbef10f36b45a36955f6819622025	no	13
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5	Non Patent Literature	Shen-2013-GenMed.pdf	405483 995fa81efc1f73cf1100b0b9d83d0a5453ec91ab	no	8
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6	Non Patent Literature	Smith-1985-NuclAcidsRes.pdf	1461477 e02f8a8b54df96278808a4cfcd436dd5239b0eb8	no	14
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9	Non Patent Literature	Strom-2005-MutatRes.pdf	686611 4b44dff8cf2a56123b86fef1f9d1772bdd1a5750	no	8
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17	Non Patent Literature	Veeneman-2012-BMCBioinformatics.pdf	1122602 c8c11834f06bd911cbf3533fed4830329e5a06eb	no	8
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23	Non Patent Literature	Yershov.pdf	2169403 4c508766a534413e46703ae0d481df9bf50d2d0b	no	6
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24	Non Patent Literature	Yoon-2014-NuclAcRes.pdf	1362007 2e86e26d7098222569c815e720dabba63698ebb2	no	9
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25	Non Patent Literature	Zhou-2014-Bioinformatics.pdf	814470 dd4a58e3b2c5f96b58e4408d8b3f4718e2bb621a	no	13
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26	Non Patent Literature	Zuckerman-1987-NuclAcidsRes.pdf	1331481 fd594a38248dee553573220158 34cc0615237036	no	17
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27	Information Disclosure Statement (IDS) Form (SB08)	Information_Disclosure_Statement_Fillable_PDF_1_of_3.pdf	1041500 1ea2b8e6846b0ce50558fb3967e6842f34f24d59	no	19
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28	Information Disclosure Statement (IDS) Form (SB08)	Information_Disclosure_Statement_Fillable_PDF_2_of_3.pdf	1037408 2065de0aab5cce73cb4d2b6d75d6c4b2b2d4afbe	no	8
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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	13266862
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	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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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.

☒ A certification statement is not 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)	2018-07-11
Name/Print	Thomas C. Meyers	Registration Number	36,989

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	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

	40	Heger, 2006, Protonation of Cresol Red in Acidic Aqueous Solutions Caused by Freezing, J Phys Chem B 110 (3):1277-1287	
	41	Heid, 1996, Real time quantitative PCR, Genome Res 6:986-994	
	42	Hiatt, 2013, Single molecule molecular inversion probes for targeted, high-accuracy detection of low-frequency variation, Genome Res 23:843-54	
	43	Homer et al., 2008, Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays. PLoS One 4(8):e1000167	
	44	Homer, 2009, BFAST: An alignment tool for large scale genome resequencing, PLoS ONE 4(11):e7767	
	45	Housley, 2009, SNP discovery and haplotype analysis in the segmentally duplicated DRD5 coding region, Ann Hum Genet 73(3):274-282	
	46	Illumina, 2010, De Novo assembly using Illumina reads, Technical Note (8 pages)	
	47	International Preliminary Report on Patentability for WO 2010/126614	
	48	International Search Report and Written Opinion for PCT/US12/29790, mailed June 14, 2012 17 pages	
	49	International Search Report and the Written Opinion of the International Searching Authority Mailed December 23, 2015 for International Application No. PCT/US2015/056037 (13 Pages).	
	50	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)	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference G0814.70000	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2010/001293	International filing date *(day/month/year)* 30 April 2010 (30.04.2010)	Priority date *(day/month/year)* 30 April 2009 (30.04.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GOOD START GENETICS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	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 Article 35(2) 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 01 November 2011 (01.11.2011)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Philippe Bécamel e-mail: pt01.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: PATRICK R.H. WALLER
WOLF, GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	28 OCT 2010
Applicant's or agent's file reference G0814.70000	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/01293	30 April 2010 (30.04.2010)	30 April 2009 (30.04.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - G01N 33/48 (2010.01)
USPC - 436/94

Applicant GOOD START GENETICS

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.

3. For further details, see notes to 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 Oct. 2010 (07.10.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01293

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 10/01293

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 15, 16, 19, 22-56, 64, 65, 67

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 15, 16, 19, 22-56, 64, 65, 67 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims are not formed according to the second and third sentences of Rule 6.4(a) regarding multiply dependent claims.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 15, 16, 19, 22-56, 64, 65, 67

☐ a meaningful opinion could not be formed without the sequence listing: the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01293

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 applicable, 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 1-8, and 57, directed to a method of analyzing a plurality of gene loci, comprising: contacting each of a plurality of target nucleic acids with a probe set, wherein the probe set comprises a plurality of probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids in the same strand of one of a plurality of subregions in the target nucleic acid, wherein the subregions of the target are different.

Group II: claims 9-14, 17, 18, and 66, directed to a method of genotyping a subject, comprising determining in the sequence at least a threshold number of independently isolated nucleic acids that comprise target nucleic acid sequences and differentiator tag sequences, wherein the threshold number is a number of unique combinations of target nucleic acid and differentiator tag sequences that form unique combinations, and the target nucleic acid sequence is the sequence of a genomic locus of a subject.

Group III: claims 20-21, directed to a method of determining whether a target nucleic acid has abnormal length, comprising evaluating the capture efficiency of a target nucleic acid in a sample from a subject.

Group IV: claims 58-63, directed to a method of increasing the sensitivity of a nucleic acid detection assay comprising utilizing two different preparation methods on parallel samples and assaying the sequences of the samples, using the sequence information from both determinations to evaluate the genotype of a target nucleic acid.

The inventions listed as Groups I - IV 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:

The special technical feature of the Group I claims is a method of analyzing a plurality of gene loci, comprising: contacting each of a plurality of target nucleic acids with a probe set, wherein the probe set comprises a plurality of probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids in the same strand of one of a plurality of subregions in the target nucleic acid, wherein the subregions of the target are different. The special technical feature of the Group II claims is a method of genotyping a subject, comprising determining in the sequence at least a threshold number of independently isolated nucleic acids that comprise target nucleic acid sequences and differentiator tag sequences, wherein the threshold number is a number of unique combinations of target nucleic acid and differentiator tag sequences that form unique combinations, and the target nucleic acid sequence is the sequence of a genomic locus of a subject. The special technical feature of the Group III claims is a method of determining whether a target nucleic acid has abnormal length, comprising evaluating the capture efficiency of a target nucleic acid in a sample from a subject. The special technical feature of the Group IV claims is a method of increasing the sensitivity of a nucleic acid detection assay comprising utilizing two different preparation methods on parallel samples and assaying the sequences of the samples, using the sequence information from both determinations to evaluate the genotype of a target nucleic acid.

The only common technical element shared by the above groups is that they are related to genotyping of nucleic acids in samples. This common technical element does not represent an improvement over the prior art of US 2001/0046673 A1 to French et al. (see abstract; para [0012]- wherein length of the target was abnormal due to insertion or deletion; para [0077] - allele specific hybridization using luminescence detection; para [0107] - DNA chips generally attempt to detect SNPs by measuring the extent of hybridization of DNA targets to DNA probes immobilized on the chip surface). Therefore, the inventions of Groups I - IV lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

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. 1-14, 17, 18, 57 and 66

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01293

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, 17, 18, 57 and 66	YES
	Claims	None	NO
Inventive step (IS)	Claims	17, 18, 57	YES
	Claims	1-14 and 66	NO
Industrial applicability (IA)	Claims	1-14, 17, 18, 57 and 66	YES
	Claims	None	NO

2. Citations and explanations:

Claim 66 lacks an inventive step under PCT Article 33(3) as being obvious over the article entitled 'Multiplexed genotyping with sequence-tagged molecular inversion probes' by Hardenbol et al. (hereinafter 'Hardenbol').

As per claim 66, Hardenbol discloses 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 (pg 674, col 2, para 2--25 different individuals were genotyped, pg 677, col 1, para 3), sequencing a target nucleic acid of the nucleic acid preparation (pg 674, col 2, para 3), and performing a molecular inversion probe capture reaction on the biological sample (pg 677, col 2, para 2), genotyping the target nucleic acid based on the results of the capture reaction (pg 674, col 2, para 2). Hardenbol further teaches that the MIPs are engineered such that when annealed to a target nucleic acid, a gap between the flanking regions comprises only one nucleotide for detection of a single nucleotide polymorphism (pg 674, col 1, para 2) and it would have been obvious to one skilled in the art during the polymerization reaction to add only the nucleotide that would have indicated an SNP at this locus if the molecular inversion probe captured the target nucleic acid in the biological sample to save reagents and time. It further would have been obvious to one skilled in the art to utilize the sequence information in addition to the capture reaction information to ensure accurate genotyping.

Claim 9 lacks an inventive step under PCT Article 33(3) as being obvious over US 2003/0203370 A1 to Yakhini et al. (hereinafter "Yakhini").

As per claim 9, although Yakhini does not explicitly teach 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, Yakhini discloses a method of genotyping using mass tags (abstract), wherein "As discussed above, there are generally a much smaller number of mass tags than primer sequences, and many different primers may be therefore identically labeled. Thus, fingerprinting SNPs using the CMT/PEA technique involves extracting a small fingerprint signal from complex mass spectra in which the presence of a particular mass tag may indicate extension of many different oligonucleotide primers. Moreover, even considering only SNP-characteristic primers, there may be a number of different genotypes that map to a particular mass spectrum. For example, the mass spectrum shown in FIG. 10 corresponds to mass tags removed from primers, extended as shown in FIG. 8, characteristic for the genotype S1/S1', S2/S2', S3/S3, S4/S4, S5/S5', S6/S6. However, the same mass spectrum is produced by the above-illustrated CMT/PEA technique when applied to the example genotype S1/S1', S2/S2', S3/S3', S4'/S4', S5/S5', S6/S6, as can be see noting that, in FIG. 6, the characteristic primers for polymorphism S3 610-613 carry the same mass tags as the primer sequences characteristic for polymorphism S4' 614-617 and the characteristic primers for polymorphism S3' carry the same mass tags as the primer sequences characteristic for polymorphism S4. Therefore, the genotyping assay illustrated in FIGS. 4-10 needs to be carried out in multiple assay steps in order to distinguish genotype S1/S1', S2/S2', S3/S3, S4/S4, S5/S5', S6/S6 from genotype S1/S1', S2/S2', S3'/S3', S4'/S4', S5/S5', S6/S6. Instead of hybridizing the set of oligonucleotide primers to all chromosome fragments, including fragments produced from all six polymorphisms, the chromosome fragments need to be partitioned into sets that generate unambiguous mask-tag fingerprints under the CMT/PEA assay technique". (para [0026]). Although Yakhihi does not explicitly teach the determination of a minimum or threshold number associated with the partitioning, a person skilled in the art would have desired to do so in order to enable automation of the process, in particular computerization of the partitioning into sets that generate unambiguous fingerprints, as taught by Yakhini.

----Continued in Supplemental Box------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01293

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2): Citations and Explanations

Claims 1- 5, and 7 lack an inventive step under PCT Article 33(3) as being obvious over Hardenbol in view of the article entitled 'Applications of DNA tiling arrays for whole-genome analysis' by Mockler et al. (hereinafter 'Mockler').

As per claim 1, Hardenbol discloses 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 (abstract, pg 673, col 2, para 2, Fig. 2; pg 674, col 2, para 3-1,517 loci were genotyped in a 1,517-probe multiplex analysis), 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 (Fig. 2a, b; pg 674, col 2, para 3), wherein the subregions of the target nucleic acid are different (pg 674, col 2, para 2-3--probes were generated for 1,121 SNPs. 1,517 loci were genotyped in a 1,517-probe multiplex analysis), 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 (pg 674, col 1, para 2 to pg 674, col 2, para 1), but fails to specifically disclose wherein each subregion overlaps with at least one other subregion. Mockler, however, discloses wherein each subregion overlaps with at least one other subregion (Fig. 2a). It would have been obvious to one skilled in the art to use the tiling approach of Mockler in the method of Hardenbol, as Mockler teaches wherein such an approach reduces bias (pg 2, col 1, para 4 to pg 2, col 2, para 1).

As per claim 2, the combination of Hardenbol and Mockler disclose the method of claim 1, and Mockler further teaches wherein at least one subregion entirely overlaps at least one other subregion (Fig. 2D-probes tiled at 1 base resolution (if these were MIPs, as taught by Hardenbol, at least two of the nucleotides would be flanking nucleotides and thus one subregion would entirely overlap one other subregion)).

As per claim 3, the combination of Hardenbol and Mockler disclose the method of claim 1, and Mockler discloses 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 (Fig. 2B).

As per claim 4, the combination of Hardenbol and Mockler disclose the method of claim 1, and Hardenbol discloses 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 (Fig. 2a-H1 and H2 unique to each probe).

As per claim 5, Hardenbol discloses 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 (abstract, pg 673, col 2, para 2, Fig. 2; pg 674, col 2, para 3--1,517 loci were genotyped in a 1,517 probe multiplex analysis), 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 Fig. 2a, b; pg 674, col 2, para 3), wherein the subregions of the target nucleic acid are different (pg 674, col 2, para 2-3--probes were generated for 1,121 SNPs. 1,517 loci were genotyped in a 1,517-probe multiplex analysis), 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 (pg 674, col 1, para 2 to pg 674, col 2, para 1), but fails to specifically disclose 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. Mockler, however, discloses a tiling array 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 (Fig. 2a, d). It would have been obvious to one skilled in the art to use the tiling approach of Mockler in the method of Hardenbol, as Mockler teaches wherein such an approach reduces bias (pg 2, col 1, para 4 to pg 2, col 2, para 1).

As per claim 7, the combination of Hardenbol and Mockler disclose the method of claim 1, and Hardenbol further teaches wherein the analyzing comprises genotyping a polymorphism of the target nucleic acid (abstract).

Claims 10-14 lack an inventive step under PCT Article 33(3) as being obvious over Yakhihi in view of Hardenbol.

As to claim 10, although Yakhini does not explicitly teach wherein the isolated nucleic acids are molecular inversion probe capture products, Hardenbol teaches the use of said products for the genotyping of SNP's (abstract). It would have been obvious to a person skilled in the art that the mollecular inversion probe capture products taught by Hardenbol could have substituted for the mass spectrometric tags taught by Yakhini, with a similar type of degeneracy requiring the determination of sets to generate unambiguous sequence-tag fingerprints (para [0026]) in order to scale up the procedure taught by Yakhini to a large number of target nucleic acids.

-------Continued in Subsequent Supplemental Box-------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01293

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, Hardenbol discloses a method of genotyping a subject, the method comprising:
determining the sequence of molecular inversion probe capture products (abstract, analyzed using universal sequence tag DNA microarrays), each comprising a molecular inversion probe and a target nucleic acid (Fig. 2), wherein the sequence of the molecular inversion probe comprises a differentiator tag sequence and, optionally, a primer sequence (Fig. 2a--P1,P2,Tag), and wherein the target nucleic acid is a captured genomic locus of a subject (pg 674, col 2, para 2), and genotyping the subject at the captured genomic locus based on the sequence of the captured target nucleic acid (abstract, pg 674, col 2, para 2), but fails to specifically teach 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. However, Yakhini teaches a method of genotyping a subject using target nucleic acids linked to differentiator tags (abstract), wherein unique set of tags are identified to generate unambiguous sequence-tag fingerprints (para [0026]). Although Yakhihi does not explicitly teach the determination of a minimum or threshold number associated with the partitioning, a person skilled in the art would have desired to do so in order to enable automation of the process, in particular computerization of the partitioning into sets that generate unambiguous fingerprints, as taught by Yakhini. It would have been obvious to a person skilled in the art to combine the teaching of Hardenbol with that of Yakhini in order to scale up the procedure taught by Yakhini to a large number of target nucleic acids.

As to claim 12, Hardenbol discloses 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 (Fig. 2a), wherein the target nucleic acid is a captured genomic locus of the subject (abstract, pg 674, col 2, para 2), amplifying the molecular inversion probe capture products (pg 674, col 1, para 2), and genotyping the subject by determining, for each target nucleic acid, the sequence of the target nucleic acid (abstract--analzed using unversal sequence tag DNA microarrays), but fails to specifically disclose 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. However, Yakhini teaches a method of genotyping a subject using target nucleic acids linked to differentiator tags (abstract), wherein unique set of tags are identified to generate unambiguous sequence-tag fingerprints (para [0026]). Although Yakhihi does not explicitly teach the determination of a minimum or threshold number associated with the partitioning, a person skilled in the art would have desired to do so in order to enable automation of the process, in particular computerization of the partitioning into sets that generate unambiguous fingerprints, as taught by Yakhini. It would have been obvious to a person skilled in the art to combine the teaching of Hardenbol with that of Yakhini in order to scale up the procedure taught by Yakhini to a large number of target nucleic acids.

As to claim 13, Hardenbol discloses 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 (Each amplified probe contains a unique tag sequence that is complementary to a sequence on the universal tag array; pg. 270, col 1, para 2).

As to claim 14, although neither Hardenbol nor Yakhini explcitly teaches 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, Hardenbol teaches wherein repeatability and trio accuracy were greater than 99%, which corresponds to an error rate of less than 0.01. A person skilled in the art would have known that a likelihood of ambiguity (obtaining two or more molecular inversion probe capture products with identical combinations of target and differentiator tag sequences) of the results for a genotyping assay, particularly assays associated with either prognostication of disease or of the potential utility of pharmaceuticals to treat a disease, would have been required to be at least less than 5%.

Claim 6 lacks an inventive step under PCT Article 33(3) as being obvious over Hardenbol in view of Mockler, further in view of US 2008/0280955 A1 to McCamish et al. (hereinafter 'McCamish').

As per claim 6, the combination of Hardenbol and Mockler discloses the method of claim 1, but fails to teach that which McCamish teaches, that is wherein the target nucleic acids are selected from Table 1 (Table 9- NC_000011.8 (DHCR7), NC_000016.8 (GCSH), NC_000019.8 (BCKDH), NC_000021.7 (HLCS)). As McCamish teaches that the SNPs in Table 9 are related to drug response to blood glucose regulation (para [0258], claims 1, 15), it would have been obvious to one skilled in the art to analyze the loci taught by McCamish using the combined method of Hardenbol and Mockler in order to ascertain whether a particular subject would be susceptible to drug therapy for blood glucose regulation.

Claim 8 lacks inventive step under PCT Article 33(3) as being obvious over Hardenbol, in view of Mockler, in further view of WO 2007/107717 A1 to Chamberlain et al. (hereinafter 'Chamberlain').

As per claim 8, the combination of Hardenbol and Mockler teaches the method of claim 7, but fails to specifically teach that which Chamberlain teaches, that is wherein the polymorphism is selected from Table 2 (Table 3, 4). As Chamberlain teaches that the listed SNP's are related to responsiveness to treatment with bisphosphonate (pg 4, ln 16-33), it would have been obvious to one skilled in the art to analyze the loci and polymorphisms as taught by Chamberlain using the combined method of Hardenbol and Mockler in order to determine who would be responsive to treatment with bisphosphonate.

-------Continued in Subsequent Supplemental Box------

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01293

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V.2: Citations and Explanations

Claims 17-18 meet the requirements set forth in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest 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. Hardenbol teaches a 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 (pg 674, col 2, para 2; Fig. 2), wherein the sequence of the molecular inversion probe comprises a differentiator tag sequence and, optionally, a primer sequence (Fig. 2a), amplifying the plurality of molecular inversion probe capture products (pg 674, col 1, para 2), but fails to teach: 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. Therefore, claim 17 and claim 18, which depends therefrom, meet the aforementioned requirements for the above reasons.

Claim 57 meets the requirements set forth in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest (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 subtarget nucleic acid in the plurality of sub-target nucleic acids is indicative of the length of the sub-target nucleic acid. Hardenbol discloses a 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 (pg 674, col 1, para 2), 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 (Fig. 2a, b); and
(ii) capturing a plurality of sub-target nucleic acids that are hybridized with the plurality of detection probes (pg 674, col 1, para 3 to pg 674, col 2, para 1), but fails to specifically teach (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 subtarget nucleic acid in the plurality of sub-target nucleic acids is indicative of the length of the sub-target nucleic acid. Therefore claim 57 meets the aforementioned requirements for the above reasons.

Claims 1-14, 17, 18, 57, 66, have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

TCM/AMS 29258/31 WO

PATENT COOPERATION TREATY

NOTED ON SYSTEM

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-006/01WO 29258/31	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 12/29790	International filing date *(day/month/year)* 20 March 2012 (20.03.2012)
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	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

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)

Applicant's or agent's file reference GSGE-006/01WO 29258/31	Date of mailing *(day/month/year)* 14 JUN 2012 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 12/29790	International filing date *(day/month/year)* 20 March 2012 (20.03.2012)
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-006/01WO 29258/31	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 12/29790	International filing date *(day/month/year)* 20 March 2012 (20.03.2012)	(Earliest) Priority Date *(day/month/year)* 31 March 2011 (31.03.2011)
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 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:

IDENTIFICATION OF A NUCLEIC ACID TEMPLATE IN A MULTIPLEX SEQUENCING REACTION

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/US 12/29790

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; C07H 21/04 (2012.01)
USPC - 435/6.1, 536/23.1
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)
IPC(8): C12Q 1/68; C07H 21/04 (2012.01)
USPC: 435/6.1, 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/6.11, 436/94, 536/22.1, 536/24.3, 536/24.33

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST, Google Scholar: Barcode, template, identifier, multiplex sequencing, identical, tag, validate, solution, nucleic acid, synthesis, substrate, contact, detect, polymerase, duplex, quantification, contamination, oligonucleotide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0330619 A1 (WILLIS et al.) 30 December 2010 (30.12.2010); para [0012], [0014], [0094], [0131], [0155], [0199], [0228]-[0229], [0273], [0279], [0286], [0294], [0297], [0355], [0365]	1-21
Y		22-33
Y	US 2008/0269068 A1 (CHURCH et al.) 30 October 2008 (30.10.2008); para [0009]	22-33

☐ 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
25 May 2012 (25.05.2012)	14 JUN 2012
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)*	14 JUN 2012

Applicant's or agent's file reference	FOR FURTHER ACTION
GSGE-006/01WO 29258/31	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 12/29790	20 March 2012 (20.03.2012)	31 March 2011 (31.03.2011)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C12Q 1/68; C07H 21/04 (2012.01)
USPC - 435/6.1, 536/23.1

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 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	25 May 2012 (25.05.2012)	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 12/29790

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., EX1002, p. 1288

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/29790

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	22-33	YES
	Claims	1-21	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-33	NO
Industrial applicability (IA)	Claims	1-33	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-21 lack novelty under PCT Article 33(2) as being anticipated by US 2010/0330619 A1 Willis et al. (hereinafter Willis).

Regarding claim 1, concerning a method for validating the integrity of a nucleic acid template Willis teaches the method comprising:
obtaining a solution comprising a template nucleic acid (para [0012], [0101], [0114]);
introducing an identifier nucleic acid to the solution (para [0012], attach identifiable marker);
incorporating an identical barcode oligonucleotide into the template and the identifier nucleic acids (para [0131]); and
sequencing the template and the identifier nucleic acids (para [0283], [0284]).

Regarding claim 2, Willis further teaches the method according to claim 1, wherein prior to sequencing, the template and the identifier are attached to a substrate (para [0286], [0294]).

Regarding claim 3, Willis further teaches the method according to claim 2, wherein the template and the identifier are directly attached to the substrate (para [0294], attachment or association with substrate).

Regarding claim 4, Willis further teaches the method according to claim 2, wherein the template and the identifier are indirectly attached to the substrate (para [0294], attachment or association with substrate).

Regarding claim 5, Willis further teaches the method according to claim 1, further comprising, amplifying the template and the identifier (para [0014], [0138])

Regarding claim 6, Willis further teaches the method according to claim 1, wherein sequencing is sequencing by synthesis (para [0218], [0165], [0202]).

Regarding claim 7, Wills further teaches the method according to claim 6, wherein the sequencing by synthesis is single molecule sequencing by synthesis (para [0365]).

Regarding claim 8, Willis further teaches the method according to claim 1, wherein sequencing comprises: hybridizing a primer to both the template and the identifier to form a template/primer duplex and an identifier/primer duplex (para [0012], [0138]);
contacting both duplexes with a polymerase enzyme in the presence of at least one detectably labeled nucleotide under conditions that permit the polymerase to add nucleotides to the primers of both duplexes in a template-dependent manner (para [0228]-[0229]; [0138]);
detecting a signal from the incorporated labeled nucleotide (para [0225]-[0226]); and
sequentially repeating the contacting and detecting steps at least once, wherein sequential detection of incorporated labeled nucleotide determines the sequence of the template nucleic acid and the identifier nucleic acid (para [0225]-[0226]).

Regarding claim 9, Willis further teaches the method according to claim 8, wherein the detectably labeled nucleotide is an optically labeled nucleotide (para [0199]).

Regarding claim 10, Willis further teaches the method according to claim 9, wherein the optically labeled nucleotide is a fluorescently labeled nucleotide (para [0199]).

*****Continued in Supplemental Box*****

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/29790

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 fu lly supported by the description, are made:

Claims 1-10 are objected to as being unclear as to the term "integrity". The claims fail to clearly set forth the technical features of the invention for which protection is sought, as according to PCT Rule 6. Claim 1 is generally narrative and indefinite with regard to the tem "integrity". Specifically, the claim fail to define the matter for which protection is sought with sufficient detail such that the claims are not clear and consise. Further, the specifications fails to enable one of ordinary skill in the art to practice the claims because the term is not defined nor fully supported.

Form PCT/ISA/237 (Box No. VIII) (July 2011)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/29790

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box V(2):

Regarding claim 11 concerning a method for quantifying a contamination rate in a sequencing reaction, Willis teaches the method comprising:
determining a number of barcode reads in a sequencing reaction that are correctly correlated with an identifier nucleic acid (para [0012], [0131]), wherein the identifier nucleic acid is associated with a template nucleic acid (para [0012]), and the barcode reads are generated by a sequencing apparatus (para [0094]);
determining a number of barcode reads in the sequencing reaction that are incorrectly correlated with the identifier nucleic acid (para [0297]-[0299]); and
obtaining a fraction of the two numbers, thereby quantifying a contamination rate in the sequencing reaction (para [0298]).

Regarding claim 12, Willis further teaches the method according to claim 11, wherein determining comprises:
introducing an identifier nucleic acid to a solution (para [0012], attach identifiable marker) comprising a template nucleic acid (para [0131]);
incorporating an identical barcode oligonucleotide into the template and the identifier nucleic acids (para [0131]); and
sequencing the template and the identifier nucleic acids (para [0283]).

Regarding claim 13, Willis further teaches the method according to claim 12, wherein prior to sequencing, the template and the identifier are attached to a substrate (para [0286], [0294]).

Regarding claim 14, Willis further teaches the method according to claim 13, wherein the template and the identifier are directly attached to the substrate (para [0294], attachment or association with substrate).

Regarding claim 15, Willis further teaches the method according to claim 13, wherein the template and the identifier are indirectly attached to the substrate (para [0294], attachment or association with substrate).

Regarding claim 16, Willis further teaches the method according to claim 12, further comprising, amplifying the template and the identifier (para [0014], [0138])

Regarding claim 17, Willis further teaches the method according to claim 12, wherein sequencing is sequencing by synthesis (para [0218], [0165], [0202]).

Regarding claim 18, Wills further teaches the method according to claim 17, wherein the sequencing by synthesis is single molecule sequencing by synthesis (para [0365]).

Regarding claim 19, Willis further teaches the method according to claim 12, wherein sequencing comprises: hybridizing a primer to both the template and the identifier to form a template/primer duplex and an identifier/primer duplex (para [0012], [0138]);
contacting both duplexes with a polymerase enzyme in the presence of at least one detectably labeled nucleotide under conditions that permit the polymerase to add nucleotides to the primers of both duplexes in a template-dependent manner (para [0228]-[0229]; [0138]);
detecting a signal from the incorporated labeled nucleotide (para [0225]-[0226]); and
sequentially repeating the contacting and detecting steps at least once, wherein sequential detection of incorporated labeled nucleotide determines the sequence of the template nucleic acid and the identifier nucleic acid (para [0225]-[0226]).

Regarding claim 20, Willis further teaches the method according to claim 19, wherein the detectably labeled nucleotide is an optically labeled nucleotide (para [0199

Regarding claim 21, Willis further teaches the method according to claim 20, wherein the optically labeled nucleotide is a fluorescently labeled nucleotide (para [0199]).

Claims 22-33 lack inventive step under PCT Article 33(3) as being obvious over Willis in view of 2008/0269068 A1 to Church et al. (hereinafter .Church.).

Regarding claim 22, concerning a method for identifying a contamination in a batch of barcode oligonucleotides, Willis teaches the method comprising:
preparing a plurality of batches of barcoded identifier nucleic acids, wherein each batch comprises a unique identifier nucleic acid attached to a unique barcode oligonucleotide (para [0131]); however fails to teach
pooling the batches;
sequencing the pooled batches;
and identifying barcode oligonucleotides that are improperly paired with identifier nucleic acids.
Church teaches a method of identifying a contamination in a batch of barcode oligonucleotides (para [0009], detect that barcodes have been correctly attached and thus also being able to detect incorrect attachment)
pooling the batches (para [0009]);
sequencing the pooled batches (para [0009]);
and identifying barcode oligonucleotides that are improperly paired with identifier nucleic acids (para [0009], detect that barcodes have been correctly attached and thus also being able to detect incorrect attachment). In light of the fact that Church teaches a method of confirming correct barcode attachment to an oligonucleotide attached to an identifier (para [0009]), it would have been obvious to one of ordinary skill in the art to confirm correct attachment of barcodes to the sequence of interest in order to further insure the validity of the results found in the method taught by Willis.

*****Continued in Supplemental Box*****

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 12/29790

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:
*****Continuation of Previous Supplemental Box*****

Regarding claim 23, the combination of Willis and Church makes obvious the method according to claim 22, and Willis further teaches wherein attaching comprises a PCR reaction (para [0146]).

Regarding claim 24, the combination of Willis and Church makes obvious the method according to claim 22, and Wills further teaches wherein attaching comprises a ligation reaction (para [0381]).

Regarding claim 25, the combination of Willis and Church makes obvious the method according to claim 22, and Willis further teaches wherein prior to sequencing, the barcoded identifier is attached to a substrate (para [0286], [0294]).

Regarding claim 26, the combination of Willis and Church makes obvious the method according to claim 25, and Willis further teaches wherein the barcoded identifier is directly attached to the substrate (para [0294], attachment or association with substrate).

Regarding claim 27, the combination of Willis and Church makes obvious the method according to claim 25, and Willis further teaches wherein the barcoded identifier is indirectly attached to the substrate (para [0294], attachment or association with substrate).

Regarding claim 28, the combination of Willis and Church makes obvious the method according to claim 22, and Church further teaches the method further comprising, amplifying the barcoded identifier (para [0007]).

Regarding claim 29, the combination of Willis and Church makes obvious the method according to claim 22, and Church further teaches wherein sequencing is sequencing by synthesis (para [0045]).

Regarding claim 30, the combination of Willis and Church makes obvious the method according to claim 29, and Church further teaches wherein the sequencing by synthesis is single molecule sequencing by synthesis (para [0016]).

Regarding claim 31, the combination of Willis and Church makes obvious the method according to claim 22, and Willis further teaches wherein sequencing comprises:
hybridizing a primer to the barcoded identifier to form an identifier/primer duplex (para [0012], [0138]);
contacting the duplex with a polymerase enzyme in the presence of at least one detectably labeled nucleotide under conditions that permit the polymerase to add nucleotides to the primer in a template-dependent manner (para [0228]-[0229]; [0138]);
detecting a signal from the incorporated labeled nucleotide (para [0225]-[0226]); and
sequentially repeating the contacting and detecting steps at least once, wherein sequential detection of incorporated labeled nucleotide determines the sequence of the barcoded identifier nucleic acid (para [0225]-[0226]).

Regarding claim 32, the combination of Willis and Church makes obvious the method according to claim 31, and Willis further teaches wherein the detectably labeled nucleotide is an optically labeled nucleotide (para [0199])

Regarding claim 33, the combination of Willis and Church makes obvious the method according to claim 32, and Willis further teaches wherein the optically labeled nucleotide is a fluorescently labeled nucleotide (para [0199]).

Claims 1-33 have industrial applicability under PCT Article 33(4) because the subject matter can be made or used in industry.

SEARCH HISTORY

Application Number:	PCT/US 12/29790
Search Conducted By:	MAB
Search Approved By:	RLS

US/IPC Classifications Searched:	IPC(8): C12Q 1/68; C07H 21/04 (2012.01) USPC: 435/6.1, 536/23.1; 435/6.11, 436/94, 536/22.1, 536/24.3, 536/24.33
Date Conducted:	21-25 May 2012 (21-25.05.2012)

Documentation Searched:	IPC(8): C12Q 1/68; C07H 21/04 (2012.01) USPC: 435/6.1, 536/23.1; 435/6.11, 436/94, 536/22.1, 536/24.3, 536/24.33
Search Terms Used:	Barcode, template, identifier, multiplex sequencing, identical, tag, validate, solution, nucleic acid, synthesis, substrate, contact, detect, polymerase, duplex, quantification, contamination, oligonucleotide
Date Conducted:	21-25 May 2012 (21-25.05.2012)

Electronic Database Searched:	PUBWEST
Files Searched:	USPT, PGPB, EPAB, JPAB
Date Conducted:	21-25 May 2012 (21-25.05.2012)

Search Logic

DATE: Tuesday, May 22, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L13	L12 and (barcode$4 with (templat$4 and identif$4))	1	L13	L13
L12	L11 and barcode$2	1	L12	L12
L11	L10 and identif$4	33	L11	L11
L10	L9 and templat$4	34	L10	L10
L9	L8 and multiplex sequence$2	35	L9	L9
L8	L7 or L6	73187	L8	L8
L7	(435/6.1 or 536/23.1 or 435/6.11 or 436/94 or 536/22.1 or 536/24.3 or 536/24.33).ccls.	45882	L7	L7
L6	(C12Q1/68 or C07H21/04).ipc.	44032	L6	L6

END OF SEARCH HISTORY

DATE: Tuesday, May 22, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L5	L4 and (barcode$4 with (templat$4 and identif$4))	1	L5	L5
L4	L3 and barcode$4	1	L4	L4
L3	L2 and identif$4	44	L3	L3
L2	L1 and template$2	46	L2	L2
L1	multiplex sequence$4	171	L1	L1

END OF SEARCH HISTORY

DATE: Tuesday, May 22, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L21	L20 and (identifier with barcod$4)	2	L21	L21
L20	L19 and identifier	3	L20	L20
L19	L18 and (sequencing with multiplex)	21	L19	L19
L18	L17 and multiplex	34	L18	L18

L17	L14 and sequencing	55	L17	L17
L16	L15 and sequencing	55	L16	L16
L15	L14 and sequenc$4	160	L15	L15
L14	barcod$4 with (template$3 and identif$4)	228	L14	L14

END OF SEARCH HISTORY

DATE: Tuesday, May 22, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L22	identical with barcod$4 with templat$4 with identifier$2	0	L22	L22

END OF SEARCH HISTORY

DATE: Tuesday, May 22, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L5	L4 and ((tag$4 or barcod$4) with identical with (template$2 and identifier))	3	L5	L5
L4	L1 and ((barcod$4 or tag$2) with (identical$))	59	L4	L4
L3	L1 and ((barcod$4 or tag$2) with (identical))	59	L3	L3
L2	L1 and (validat$4 with templat$4)	0	L2	L2
L1	multiplex sequencing	335	L1	L1

END OF SEARCH HISTORY

DATE: Tuesday, May 22, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L10	L9 and barcode$2	7	L10	L10
L9	L7 and identifier	12	L9	L9
L8	L7 and (identifier with solution$2)	0	L8	L8
L7	L6 and (solution with template$2)	55	L7	L7
L6	multiplex sequenc$4	500	L6	L6

END OF SEARCH HISTORY

DATE: Wednesday, May 23, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L6	L5 and substrate$2	8	L6	L6
L5	L4 and (sequenc$4 with template$2 with identif$4)	8	L5	L5
L4	L3 and identifier	10	L4	L4
L3	L2 and (solution$2 with template$2)	37	L3	L3
L2	L1 and multiplex sequenc$4	246	L2	L2
L1	nucleic acid with template$2	24689	L1	L1

END OF SEARCH HISTORY

DATE: Wednesday, May 23, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L7	L6 and barcode$2	7	L7	L7
L6	L5 and substrate$2	8	L6	L6
L5	L4 and (sequenc$4 with template$2 with identif$4)	8	L5	L5
L4	L3 and identifier	10	L4	L4
L3	L2 and (solution$2 with template$2)	37	L3	L3
L2	L1 and multiplex sequenc$4	246	L2	L2
L1	nucleic acid with template$2	24689	L1	L1

END OF SEARCH HISTORY

DATE: Wednesday, May 23, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L8	L7 and synthesis	7	L8	L8
L7	L6 and barcode$2	7	L7	L7
L6	L5 and substrate$2	8	L6	L6
L5	L4 and (sequenc$4 with template$2 with identif$4)	8	L5	L5
L4	L3 and identifier	10	L4	L4
L3	L2 and (solution$2 with template$2)	37	L3	L3

L2	L1 and multiplex sequenc$4	246	L2	L2
L1	nucleic acid with template$2	24689	L1	L1

END OF SEARCH HISTORY

DATE: Wednesday, May 23, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L20	L19 and substrate$2	12	L20	L20
L19	L18 and solution$2	12	L19	L19
L18	L17 and (nucleic acid$2 with templat$4)	12	L18	L18
L17	L16 and (contact$4 with detect$4)	12	L17	L17
L16	L15 and polymerase$2	14	L16	L16
L15	L13 and duplex	14	L15	L15
L14	L13 and duplez	0	L14	L14
L13	L12 and (primer$2 with identifier$2)	22	L13	L13
L12	L11 and (primer$2 with template$2)	260	L12	L12
L11	multiplex sequencing	335	L11	L11
L10	L9 and (primer$2 with identifier$2)	0	L10	L10
L9	L8 and (primer$2 with template$2)	7	L9	L9
L8	L7 and synthesis	7	L8	L8
L7	L6 and barcode$2	7	L7	L7
L6	L5 and substrate$2	8	L6	L6
L5	L4 and (sequenc$4 with template$2 with identif$4)	8	L5	L5
L4	L3 and identifier	10	L4	L4
L3	L2 and (solution$2 with template$2)	37	L3	L3
L2	L1 and multiplex sequenc$4	246	L2	L2
L1	nucleic acid with template$2	24689	L1	L1

END OF SEARCH HISTORY

DATE: Wednesday, May 23, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L7	L6 and (barcode$2 with template$2 and (identifier$4 or tag$4))	13	L7	L7
L6	L5 and ((identifier$4 or tag$4) with templat$4)	50	L6	L6
L5	L4 and template$2	99	L5	L5
L4	L1 and contaminat$4	102	L4	L4

L3	L1 and contamination	71	L3	L3
L2	L1 and (quantif$4 with contamination)	0	L2	L2
L1	multiplex sequencing	335	L1	L1

END OF SEARCH HISTORY

DATE: Thursday, May 24, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L6	L2 and ((improper$4 or incorrect$4) with pair$4)	1	L6	L6
L5	L4 and ((improper$4 or incorrect$4) with pair$4)	0	L5	L5
L4	L3 and sequenc$4	8	L4	L4
L3	L2 and ((marker$2 or identifier$2) with barcode oligonucleotide$2)	8	L3	L3
L2	barcode$2 with oligonucleotide$2	199	L2	L2
L1	contamination with barcode$2 with oligonucleotide$2	0	L1	L1

END OF SEARCH HISTORY

DATE: Thursday, May 24, 2012 Purge Queries Printable Copy Create Case

Set Name Side by Side	Query	Hit Count	Set Name Result Set	Set Name Grid
	DB=PGPB,USPT,USOC,EPAB,JPAB; PLUR=NO; OP=ADJ			
L12	improper$4 with pair$4 with barcode$2	0	L12	L12
L11	L9 and (improper$4 with pair$4)	0	L11	L11
L10	L9 and (improper$4 with pair$2)	0	L10	L10
L9	identif$4 with barcode with oligonucleotide$2	42	L9	L9
L8	identif$4 with barcode with oligonucleotide$2 with improper$4	0	L8	L8
L7	identif$4 with barcode with oligonucleotide$2 with improper$4 with pair$4	0	L7	L7

END OF SEARCH HISTORY

Electronic Database Searched	Google
Files Searched	Scholar
Date Conducted	21-25 May 2012 (21-25.05.2012)

Search Logic:

About 285 results (**0.10** sec) multiplex sequencing and identical barcode on template and identifier
About 129 results (**0.16** sec) validate integrity of nucleic acid template in multiplex sequencing and barcodes
About 1,520 results (**0.13** sec) validation of nucleic acid template and barcode
About 534 results (**0.10** sec) validation of nucleic acid template and barcode and multiplex sequencing
About 71 results (**0.11** sec) validate integrity of a NA template in a multiplex sequence reaction and barcode
About 1,590 results (**0.10** sec) validate integrity of a NA template in a multiplex sequence reaction
About 36 results (**0.08** sec) multiplex sequencing and validate integrity of a NA template in a multiplex sequence reaction and barcode
About 1,880 results (**0.09** sec) multiplex sequencing and template and identifier sequence
About 946 results (**0.13** sec) validate integrity of nucleic acid template and quantify contamination rate of multiplex sequencing
About 59 results (**0.13** sec) validate integrity of nucleic acid template and quantify contamination rate of multiplex sequencing and identical barcodes
About 492 results (**0.12** sec) quantify contamination rate of multiplex sequencing and identical barcodes
About 1,020 results (**0.10** sec) identify contamination in a batch of barcode oligonucleotides
About 143 results (**0.10** sec) identify improper pairing of barcodes and oligonucleotides
About 1,210 results (**0.13** sec) determine identify improper pairing of barcodes
About 412 results (**0.09** sec) incorrect pairing of barcode oligonucleotide
About 4,350 results (**0.37** sec) synthesis of oligonucleotide barcodes
About 1,630 results (**0.10** sec) synthesis of oligonucleotide barcodes contamination
About 2,130 results (**0.11** sec) barcode oligonucleotide contamination
About 3,850 results (**0.14** sec) barcode oligonucleotide and correct pairing
About 85 results (**0.10** sec) identify improperly paired barcode oligonucleotides
About 5,160 results (**0.14** sec)paired barcode oligonucleotide and sequencing

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)*	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
Facsimile No. 82-42-472-7140	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 : **2016.06.23**) 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 : **AC64X2X9**

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-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., EX1002, p. 1302

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
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		CA 2821906 A1	28/06/2012
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		EP 2473638 A1	11/07/2012
		EP 2572003 A1	27/03/2013
		EP 2656263 A2	30/10/2013
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		EP 2854056 A2	01/04/2015
		EP 2854056 A3	03/06/2015
		EP 2854057 A2	01/04/2015
		EP 2854057 A3	26/08/2015
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		EP 2902500 A1	05/08/2015
		IL 227842 D0	30/09/2013
		JP 2014-502845 A	06/02/2014
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		RU 2013-141237 A	20/03/2015
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		US 9163282 B2	20/10/2015
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		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

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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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Previous Page

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

Petitioner Illumina, Inc., EX1002, p. 1311

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 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
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)* 04 FEB 2014
Applicant's or agent's file reference GSGE-014/01 WO 29258/64	**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.

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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.

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   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

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INTERNATIONAL SEARCHING AUTHORITY

To: Thomas C. Meyers
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Boston, MA 02111
United States of America

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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
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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

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   ☐ 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.

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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

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-***-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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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).

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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)	2018-07-11
Name/Print	Thomas C. Meyers	Registration Number	36,989

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	1	International Search Report and Written Opinion for PCT/US13/61691 mailed January 10, 2014 (10 pages)	
	2	International Search Report and Written Opinion for PCT/US2013/036575 dated August 12, 2013, 10 pages.	
	3	International Search Report and Written Opinion for PCT/US2013/044039 mailed 01 November 2013, (15 pages)	
	4	International Search Report and Written Opinion for PCT/US2015/056037 mailed 12/23/15; 11 pages	
	5	International Search Report and Written Opinion for WO 2010/126614	
	6	International Search Report and Written Opinion issued January 29, 2015 in counterpart PCT Application No. PCT/US14/61138	
	7	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)	
	8	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)	
	9	International Search Report and Written Opinion mailed January 22, 2016, for International Patent Application No. PCT/US2015/050964, filed September 18, 2015 (6 pages).	
	10	International Search Report and Written Opinion mailed January 7, 2015, for International Patent Application No. PCT/US14/60256, filed October 13, 2014 (9 pages)	
	11	International Search Report and Written Opinion mailed May 4, 2016, for International patent application No. PCT/US2016/012286 with international filing date January 6, 2015 (7 pages)	

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	12	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)	
	13	International Search Report and Written Opinion mailed on January 29, 2015, for Patent Application No. PCT/US14/61138, filed October 17, 2014, (11 pages)	
	14	International Search Report and Written Opinion mailed on January 29, 2015, for Patent Application No. PCT/US2014/060056, filed October 10, 2014, (14 pages)	
	15	International Search Report and Written Opinion mailed on June 28, 2013, for Patent Application No. PCT/US2013/032885, filed March 19, 2013, (9 pages)	
	16	International Search Report and Written Opinion mailed on March 18, 2015, for Patent Application No. PCT/US14/40516, filed June 2, 2014 (16 pages)	
	17	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).	
	18	International Search Report and Written Opinion mailed September 2, 2015 for International Patent Application No. PCT/US2015/030366, filed May 12, 2015 (12 pages)	
	19	International Search Report and Written Opinion of the International Searching Authority mailed December 13, 2016 for International Application No. PCT/US2016/051928 (14 Pages).	
	20	International Search Report and Written Opinion of the International Searching Authority mailed June 12, 2017 for International Application No. PCT/US2017/016498 (12 Pages).	
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	50	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	

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.

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., EX1002, p. 1333

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:

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:

- ☒ 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 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
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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.

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.

Form PCT/ISA/210 (first sheet) (July 2009)

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:

- ☒ 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	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:

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.

Petitioner Illumina, Inc., EX1002, p. 1358

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., EX1002, p. 1366

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

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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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of : Previous Page

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

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference G0814.70000	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/01293	International filing date *(day/month/year)* 30 April 2010 (30.04.2010)	(Earliest) Priority Date *(day/month/year)* 30 April 2009 (30.04.2009)
Applicant GOOD START GENETICS		

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. 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/US 10/01293

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.: 15, 16, 19, 22-56, 64, 65, 67
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 1-8, and 57, directed to a method of analyzing a plurality of gene loci, comprising: contacting each of a plurality of target nucleic acids with a probe set, wherein the probe set comprises a plurality of probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids in the same strand of one of a plurality of subregions in the target nucleic acid, wherein the subregions of the target are different.

- Please see extra sheet for continuation -

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.:
1-14, 17, 18, 57 and 66

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.:

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 10/01293

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G01N 33/48 (2010.01)
USPC - 436/94
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- 436/94

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, Google Scholar
Search Terms:molecular inversion probe, multiplex, overlap, tile, stack, probe, DNA, bias, reduce, circular, padlock, genotyping, probe set

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	Hardenbol et al., 'Multiplexed genotyping with sequence-tagged molecular inversion probes' Nature Biotechnology, 2003, Vol. 21, No. 6, pages 673-678; abstract, Fig. 2; pg 673, col 2, para 2pg 674, col 1, para 2-3; pg 674, col 2, para 1-3; pg 677, col 1, para 3	66 ---- 1-8, 10-14 ---------- 17-18, 57
X --- Y	US 2003/0203370 A1 (YAKHINI et al.) 30 October 2003 (30.10.2003) abstract, para [0026]	9 ------- 10-14
Y	Mockler et al., 'Applications of DNa tiling arrays for while-genome analysis', Genomics, 2005, Vol. 85, pages 1-15; Fig. 2; pg 2, col 1, para 4 to pg 2, col 2, para 1	1-8
Y	US 2008/0280955 A1 (MCCAMISH et al), 13 Nov. 2008 (13.11.2008), Table 9, para [0258], claims 1, 15	6
Y	WO 2007/107717 A1 (CHAMBERLAIN et al) 27 Sep. 2007 (27.09.2007), Tables 3, 4; pg 4, ln 16-33	8
&	US 2010/0129896 A1 (KNAPP) 27 May 2010 (27.05.2010)	57

☐ 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 Oct. 2010 (15.10.2010)	28 OCT 2010
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 10/01293

Continuation of Box III: Unity of Invention

Group II: claims 9-14, 17, 18, and 66, directed to a method of genotyping a subject, comprising determining in the sequence at least a threshold number of independently isolated nucleic acids that comprise target nucleic acid sequences and differentiator tag sequences, wherein the threshold number is a number of unique combinations of target nucleic acid and differentiator tag sequences that form unique combinations, and the target nucleic acid sequence is the sequence of a genomic locus of a subject.

Group III: claims 20-21, directed to a method of determining whether a target nucleic acid has abnormal length, comprising evaluating the capture efficiency of a target nucleic acid in a sample from a subject.

Group IV: claims 58-63, directed to a method of increasing the sensitivity of a nucleic acid detection assay comprising utilizing two different preparation methods on parallel samples and assaying the sequences of the samples, using the sequence information from both determinations to evaluate the genotype of a target nucleic acid.

The inventions listed as Groups I - IV 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:

The special technical feature of the Group I claims is a method of analyzing a plurality of gene loci, comprising: contacting each of a plurality of target nucleic acids with a probe set, wherein the probe set comprises a plurality of probes, each probe having a central region flanked by a 5' region and a 3' region that are complementary to nucleic acids in the same strand of one of a plurality of subregions in the target nucleic acid, wherein the subregions of the target are different. The special technical feature of the Group II claims is a method of genotyping a subject, comprising determining in the sequence at least a threshold number of independently isolated nucleic acids that comprise target nucleic acid sequences and differentiator tag sequences, wherein the threshold number is a number of unique combinations of target nucleic acid and differentiator tag sequences that form unique combinations, and the target nucleic acid sequence is the sequence of a genomic locus of a subject. The special technical feature of the Group III claims is a method of determining whether a target nucleic acid has abnormal length, comprising evaluating the capture efficiency of a target nucleic acid in a sample from a subject. The special technical feature of the Group IV claims is a method of increasing the sensitivity of a nucleic acid detection assay comprising utilizing two different preparation methods on parallel samples and assaying the sequences of the samples, using the sequence information from both determinations to evaluate the genotype of a target nucleic acid.

The only common technical element shared by the above groups is that they are related to genotyping of nucleic acids in samples. This common technical element does not represent an improvement over the prior art of US 2001/0046673 A1 to French et al. (see abstract; para [0012]- wherein length of the target was abnormal due to insertion or deletion; para [0077] - allele specific hybridization using luminescence detection; para [0107] - DNA chips generally attempt to detect SNPs by measuring the extent of hybridization of DNA targets to DNA probes immobilized on the chip surface). Therefore, the inventions of Groups I - IV lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

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-020/01WO 29258/108	Date of mailing *(day/month/year)* 29 JAN 2015 **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.

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 -

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

89958/138

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

Petitioner Illumina, Inc., EX1002, p. 1399

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

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Form PCT/ISA/210 (second sheet) (April 2005)

Petitioner Illumina, Inc., EX1002, p. 1400

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., EX1002, p. 1401

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., EX1002, p. 1405

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

Petitioner Illumina, Inc., EX1002, p. 1406

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., EX1002, p. 1407

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):

- 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

Petitioner Illumina, Inc., EX1002, p. 1409

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

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.

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 GSGE-026/01WO 29258/145	**FOR FURTHER ACTION** 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:

Petitioner Illumina, Inc., EX1002, p. 1431

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., EX1002, p. 1432

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.

Petitioner Illumina, Inc., EX1002, p. 1434

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:

Petitioner Illumina, Inc., EX1002, p. 1438

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., EX1002, p. 1439

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).

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 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

Petitioner Illumina, Inc., EX1002, p. 1441

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

Petitioner Illumina, Inc., EX1002, p. 1442

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).

Petitioner Illumina, Inc., EX1002, p. 1443

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	FOR FURTHER ACTION
GSGE-018/01WO 29258/100	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:

- [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	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.
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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)).

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

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.**
Continuation of:

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).

Petitioner Illumina, Inc., EX1002, p. 1454

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/060056

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

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).

Petitioner Illumina, Inc., EX1002, p. 1455

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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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).

Petitioner Illumina, Inc., EX1002, p. 1456

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2014/060056

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

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.

Petitioner Illumina, Inc., EX1002, p. 1457

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.

Petitioner Illumina, Inc., EX1002, p. 1458

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.

Petitioner Illumina, Inc., EX1002, p. 1464

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

Petitioner Illumina, Inc., EX1002, p. 1465

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).

Petitioner Illumina, Inc., EX1002, p. 1466

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 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:

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

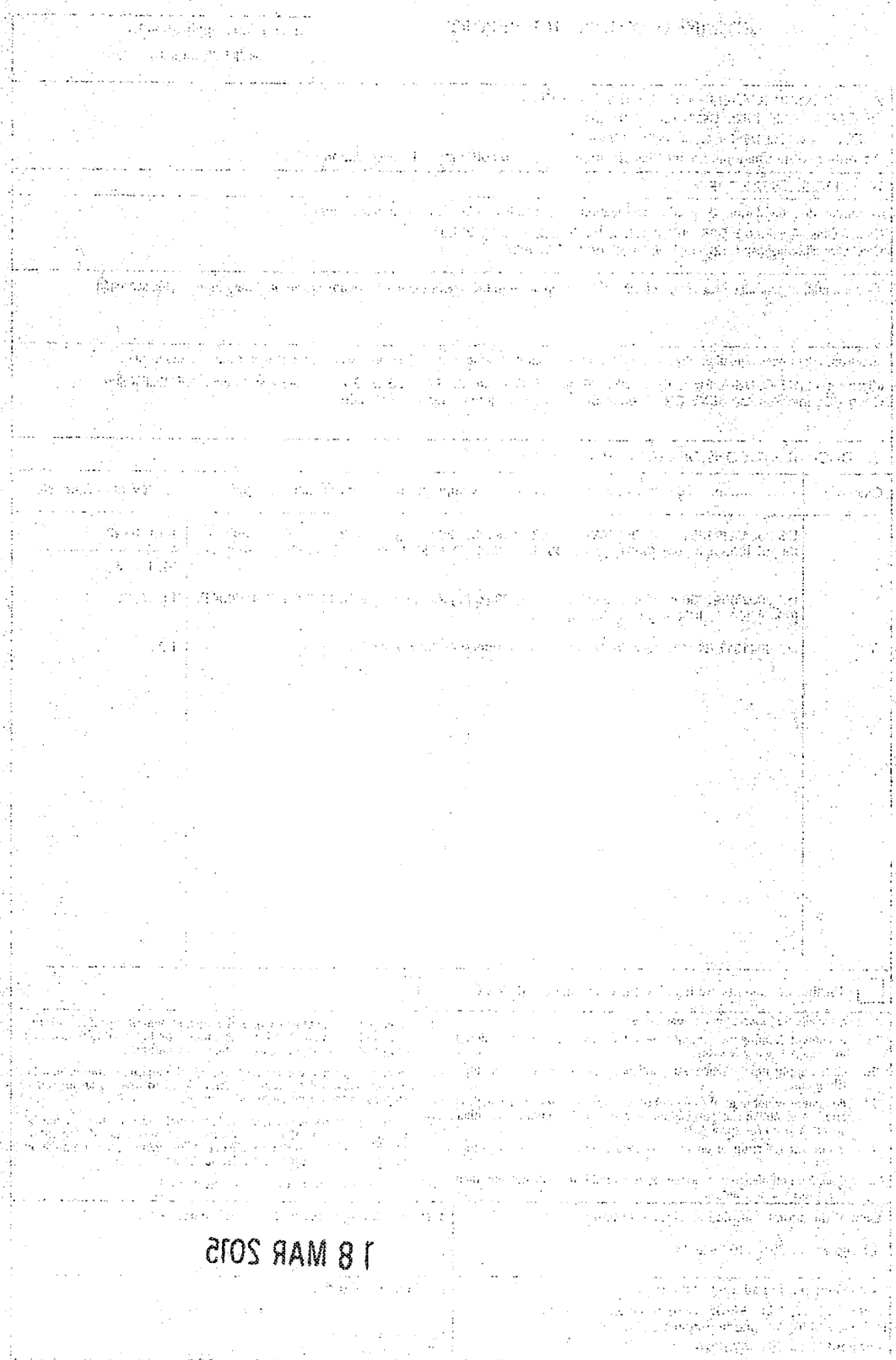
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0171051 A1 (HOLLOWAY, J) 02 September 2004; Figures 1, 2, 7, 8A; Paragraphs [0030], [0031], [0054], [0061], [0062], [0112], [0118], [0127]-[0129], [0133], [0150], [0154], [0212]	1-13, 16-22
Y		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

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 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-***-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US14/40516

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
-***-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	(19 AND 20) NOT 22	9/17/2014
22	319 hits	Combined query	20 AND 21	9/17/2014
21	2093 hits	Full text and claims Database Years	((DNA OR nucle* OR geno*) ADJ4 (sequen* OR string*)) NEAR10 (compress* USPAT,USOCR,EPO,JPO,DERWENT,IBM_TDB 1836-2014	9/17/2014
20	136954 hits	Claims, Title, or Abstract Database Years	(RNA* OR (genetic* OR match* OR "sequ*") AND (sequenc* OR string*) AND (detect* OR find* OR detect* OR extract* OR parse*) USPAT,USPGPUB,EPO,JPO,DERWENT,IBM_TDB 1836-2014	9/17/2014
19	5 hits	Combined query	(4 OR 5 OR 9) 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 text and claims Database Years	((DNA OR nucle*) ADJ4 (sequen* OR string*)) NEAR10 (compress* USPAT,USOCR,EPO,JPO,DERWENT,IBM_TDB 1836-2014	9/17/2014
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 text and claims Database Years	(archiv* OR compress* OR (save)* OR retrieve*) NEAR20 (sequ* OR strand* OR dna* OR volume*) USPAT,USOCR,EPO,JPO,DERWENT,IBM_TDB 1836-2014	9/17/2014

#	results	criteria	mark
12	401283 hits	Combined query	9 OR 10 OR 11	9/15/2014
11	237796 hits	Any Class Number Database Years	C12Q1/6869 USPAT,USOCR,EPO,JPO,DERWENT,IBM_TDB 1836-2014	9/15/2014
10	254052 hits	Any Class Number Database Years	C12N15/1006 USPAT,USOCR,EPO,JPO,DERWENT,IBM_TDB 1836-2014	9/15/2014
9	3404 hits	Any Class Number Database Years	G06F19/22 USPAT,USOCR,EPO,JPO,DERWENT,IBM_TDB 1836-2014	9/15/2014
8	134 hits	Combined query	6 AND 7	9/15/2014

7	61473 hits	Full text+OCR	((FASTA OR FASTQ OR SAM OR ILPAC) AND (freeze* OR remov* OR compress* OR (de ADJ duplicat*)) (HEARING Hile* OR sequenc* OR data))	9/15/2014
		Database	USPGPUB; USPAT; USOCR	
		Years	1976-2014	
6	8855 hits	Title or Abstract	((duplicat* OR identic* OR match*) AND (sequence* OR string*) AND (identif* OR find* OR detect*))	9/15/2014
		Database	USPGPUB; USPAT; USOCR	
		Years	1976-2014	
5	13928 hits	Title or Abstract	((duplicat* OR repet* OR repeat* OR identic* OR match* OR copy OR copies OR redundan*) AND (sequence* OR string*) OR array*) OR code) AND ((identif* OR locat* OR find* OR detect*) AND (obtain* OR read* OR extract* OR pars* OR review*))	9/15/2014
		Database	USPGPUB; USPAT; USOCR	
		Years	1976-2014	
4	16508 hits	Title or Abstract	((duplicat* OR repet* OR repeat* OR identic* OR match* OR copy OR copies OR redundan*) AND (sequence* OR string*) OR array*) OR characters OR chars OR letters OR code) AND (identif* OR locat* OR find* OR match* OR detect* OR slippy* OR scratch*) AND (obtain* OR read* OR extract* OR parse* OR pars* OR review*) AND (dna* OR rna* OR nucl* OR acid*))	9/15/2014
		Database	USPGPUB; USPAT; USOCR	
		Years	1976-2014	
3	9 hits	Assignee Name	GOOGLE STARLIGHT*	9/15/2014
		Claims, Title or Abstract	(sequen* AND (duplicat* OR redundan* OR match* OR identic*))	
		Database	USPGPUB; USPAT; USOCR	
		Years	1976-2014	
2	30 hits	Assignee Name	GOOGLE STARLIGHT*	9/15/2014
		Claims, Title or Abstract	sequen*	
		Database	USPGPUB; USPAT; USOCR	
		Years	1976-2014	
1	12 hits	Claims, Title or Abstract	GENOMI*	9/15/2014
		Inventor(s)	(KENNEDY HEARZ Caleb) OR (CHENHAORUI HEARZ Jiang)	
		Database	USPGPUB; EPO; JPO; DERWENT; IBM_TDB	
		Years	1976-2014	

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*

Clark Hunter LLP
MAR 29 2016
One Financial Center
Boston, Massachusetts 02111

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 2985/125	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., EX1002, p. 1491

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., EX1002, p. 1492

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., EX1002, p. 1493

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., EX1002, p. 1496

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., EX1002, p. 1497

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.

Veuillez noter que les ouvrages de la littérature non-brevets qui sont cités, par exemple les documents scientifiques ou techniques, etc., peuvent être protégés par des droits d'auteur et/ou toute autre protection des écrits prévue par les législations applicables. Les textes ainsi protégés ne peuvent être reproduits ni utilisés dans d'autres publications électroniques ou imprimées, ni rediffusés sans l'autorisation expresse du titulaire du droit d'auteur.

Please be aware that cited works of non-patent literature such as scientific or technical documents or the like may be subject to copyright protection and/or any other protection of written works as appropriate based on applicable laws. Copyrighted texts may not be copied or used in other electronic or printed publications or re-distributed without the express permission of the copyright holder.

XS CPRTENFRDE

BNSDOCID: <XS_____2006100103CF_I_>

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., EX1002, p. 1509

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

Petitioner Illumina, Inc., EX1002, p. 1510

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., EX1002, p. 1511

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

Continued on The Next Page

Petitioner Illumina, Inc., EX1002, p. 1512

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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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., EX1002, p. 1513

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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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

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In case the space in any of the preceding boxes is not sufficient.
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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).

Petitioner Illumina, Inc., EX1002, p. 1515

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., EX1002, p. 1519

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

Petitioner Illumina, Inc., EX1002, p. 1520

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., EX1002, p. 1521

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.
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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

Petitioner Illumina, Inc., EX1002, p. 1523

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
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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
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		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.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)

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:

- ☒ 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	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

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.
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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.
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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

In case the space in any of the preceding boxes is not sufficient.
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).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
The previous supplemental box - Box V No 2 (citations and explanations)

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	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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)	2018-07-11
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

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)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
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EFS ID:	33141237
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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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Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 29258/20
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15	Non Patent Literature	PCTUS2017016498_-_ISRWO.pdf	1356117 a25bd8bf1abdaedbe163bb2e601c806a9ac1dabd	no	12
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16	Non Patent Literature	PCTUS1255362_SearchReport.pdf	918900 c55267b9962b6fd9abe576fb4ea42c3242fa53ae	no	15
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17	Non Patent Literature	Isosomppi-2009-MolVis.pdf	2814941 d2e712b0065e61a8fb0a085aa3875d0572ff2807	no	13
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19	Non Patent Literature	29168_244US_-_Kambara-1988-BioTechnol_11.pdf	621210 2cf3332011ffb01f16b98f26009ec98f8564df35	no	6
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20	Non Patent Literature	Kennedy-2013-ASHGmtg.pdf	144805 68b3e8e0a071207ea92fa1e57e9ac0acfc670355	no	2
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21	Non Patent Literature	Kerem.pdf	931536 efb6ea83c278304e54fdc9fce448e1317d5ff97f	no	8
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29	Non Patent Literature	Li-2014-JAMIA.pdf	1821202 4ef554bb4dadc938cc63c535325e8364deec188e	no	11
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30	Non Patent Literature	Lin-2008-Bioinformatics.pdf	662777 b3f645a0fe765463b471c5a0edd3a48698940be6	no	7
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31	Non Patent Literature	Lin-2010-BMCGenomics.pdf	768720 0de214d3b5850e464c0ceb41eb0165d69ac758f9	no	14
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32	Non Patent Literature	Liu-2012-JBiomedBiotech.pdf	1253005 40e600e8182f5a292dc1663ebb81ab07b83e6768	no	12
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33	Non Patent Literature	Llopis-1998-PNAS.pdf	331302 2b2d4fffb6680b1cf3acd89141fed9b8b6cd8853	no	6
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34	Non Patent Literature	Ma-2006-JAmSoc.pdf	319616 dfc0bd06c97d08a3f286421e398ad0df20412863	no	15
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35	Non Patent Literature	MacArthur-2014-Nature.pdf	165833 5c474c203c526e507aee6fc16bf2ca6e6e587ac2	no	8
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36	Non Patent Literature	Maddalena-2005-GenetMed.pdf	141876 73d5693d54f3c117e97949a0c7c58f8ccf14e6f3	no	13
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37	Non Patent Literature	Malewicz-2010-ProcACM.pdf	220919 16fdc92e07caaf7f961d1940f024128dc0218acd	no	11
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38	Non Patent Literature	McDonnell.pdf	60837 009fc900237fef2078faead37164854d2b87dc4b	no	1
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39	Non Patent Literature	McKenna-2010-GenomeRes.pdf	788350 129c21c36fd1b6da57b0f3fa17774822f0617015	no	7
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40	Non Patent Literature	Meyer-2007-NAR.pdf	1154866 36c47fdd6ea4a03ee2bba690733b57ba3b56d0b8	no	5
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41	Non Patent Literature	Meyer-2008-NatProt.pdf	1114172 211daa6923591dd47a33621e034497d3e67fdd0f	no	12
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43	Non Patent Literature	Miller-2010-Genomics.pdf	2695395 1e56c4d1143ed58b74eb13a551e76f3a93d4bf47	no	13
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44	Non Patent Literature	Nucl_Acids_Res-2004-Miner-e135.pdf	223972 07cb77de071ce9386df47eb89a0e074d44b66841	no	4
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45	Non Patent Literature	Miyazaki-2009-JHG.pdf	237885 d865b381678baf29445ce78b57a13b1faa9fa88a	no	4
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Information:					
46	Non Patent Literature	Mohammed-2012-Bioinformatics.pdf	462222 d68ac1280182c44623a695ed908745a7c1f850d8	no	3
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58	Non Patent Literature	Porreca-2013-ASHGmtg.pdf	162701 df35b09b9cc1591074f7e5ab3722312271eb21f0	no	2
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60	Non Patent Literature	Richards-2008-GenetMed.pdf	10248379 71f1950cdc9661ccc7ffd79074361021a46a1438	no	7
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			Total Files Size (in bytes):	105428400	

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	GSGE-002/01US 29258/20	6082

21710 7590 10/11/2018

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
10/11/2018	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.** 13/266,862	**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 5/9/2018.

☐ 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) See Continuation Sheet is/are pending in the application.

5a) Of the above claim(s) See Continuation Sheet is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1 and 3-4 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 4/8/2013 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., EX1002, p. 1571

Continuation of Disposition of Claims* 5) Claim(s) is/are pending in the application: 1,3-4,12-16,20-30,33,36-38,40-47 and 50-56

Continuation of Disposition of Claims* 5a) Of the above claim(s) is/are withdrawn from consideration: 12-16,20-30,33,36-38,40-47 and 50-56

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Continued Examination Under 37 CFR 1.114

2. 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 5/9/2018 has been entered.

Claim Status and Formal matters

This action is in response to papers filed 5/9/2018.

Claims 1, 3-4, 12-16, 20-30, 33, 36-38, 40-47 and 50-56 are pending.

Claims 2, 5-11, 17-19, 31-32, 34-35, 39-38, 48-49 and 57-67 have been canceled.

Claims 12-16, 20-30, 33, 36-38, 40-47 and 50-56 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention , there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/3/2012.

Claims 1, 3-4 are being examined.

Claim 1 has been amended.

The previous 112-2nd rejections have been amended in view of the amendment to the claims.

The objection to the specification has been withdrawn in view of the amendment.

The 103 rejection has been withdrawn upon further consideration.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 7/11/2018 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) 1, 3-4 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Akhras et al (PLOS one (2007) volume 2 (9) e915 and supplemental table) (IDS 3/28/2013).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

Akhras teaches, "The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay [17], which includes: i) probe hybridization, single "G" base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by relinearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target (Figure 1B). The 39end of the probe, which we call the Extension Site (ES), primes for polymerization, while the 59end serves as point of ligation and is referred to as the Anchor Site (AS) (Figure 1). With all four dNTPs present, the polymerase is capable of extending past the intended point of ligation, generating a false negative. To address this problem, probes were designed to have an annealing temperature of approximately 5 degrees higher for the AS than that of the ES. The AS therefore blocks DNA extension when using a polymerase deficient in strand displacement at an appropriate intermediate temperature (50uC). For enhanced sensitivity and specificity a vast variety of probe concentrations and thermoprofiles were explored. Probes used in the 10–100 fmol concentration range yielded the strongest signal. Higher cycle numbers and shorter annealing times created a more efficient thermoprofile. The CIPer method successfully genotyped 1 pg of plasmid DNA in the presence of 200 ng non-reacting human genomic DNA, without generating any false positives (Figure S1). Assay optimizations were based on genotyping of HPV plasmid 56, validated by either SYBR GREEN assay or agarose gel electrophoresis, followed by Pyrosequencing verification (see Results, The Conserved Sequence Primer Connector Inversion Probe (CSP-CIPer))."

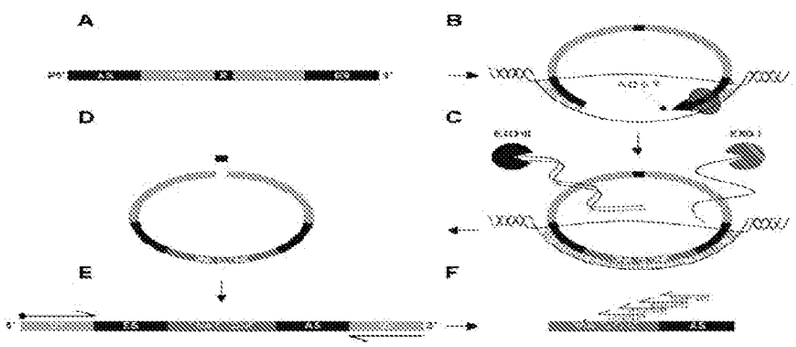


Figure 1. Schematic overview of Connector Inversion Probe (CIPer) technology. A) Synthetic oligonucleotide containing regions i) *AS and ES* (anchor site and extension sites; approximately 20 base pair fragments homologous to regions flanking target of interest, ii) *R*: restriction site for probe linearization, iii) *U1 and U2*: universal primer regions for inverted probe amplification. B) Target rescue through complete gap filling by a DNA polymerase and ligation-based probe circularization. C) Circular DNA enrichment through degradation of linear DNA by enzymes Exonuclease I and III, which are deactivated prior to the next step. D) Probe linearization by restriction site cleavage. E) Inverted probes are amplified with universal primers; one is biotinylated for subsequent amplicon validation. F) Amplicon validation using multiple sequencing primers.
doi:10.1371/journal.pone.0008915.g001

With regards to claims 1, 3 and 5, Akhras teaches, "CIPer detection was also applied to screening of resistance mutations in Neisseria gonorrhoeae. Two CIPers were used to perform a duplex amplification in a single-tube of the genes gyrA and parC [23], which are known to mutate easily and by specific SNPs generate resistance to ciprofloxacin and other quinolone antibiotics. The CIPers were designed with CIP creator 1.0.1 (http://bioel.stanford.edu/CIPer) based on previously described PCR primer-pairs not originally intended for multiplex PCR [21]. We intentionally inverted the gyrA CIPer to target the negative strand, while the parC CIPer targeted the positive strand, to illustrate that CIPers can be used on both DNA strands. In the case of close target proximities, it might be wise to revise such a strategy. Mutations on amino acid residues S91 and D95 for gyrA, and E91 for parC were the particular subjects of our interrogation. There are many other candidate genes for future CIPer-based epidemiological studies of antibiotic resistance [31]."

Thus CIPer probes to two different resistance mutations in two different Neisseria gonorrhoeae genes do not overlap in the 5' region and the 3' region (supplemental table).

Thus Akhras teaches providing a sample comprising a target nucleic acid (DNA clone), contacting the sample with a plurality of probes that flank to two different resistance mutations in two different Neisseria gonorrhoeae genes of the Neisseria gonorrhoeae chromosome do not overlap in the 5' region and the 3' region, converting the hybridized probe to a plurality of circularized probes comprising the target sequences, isolating the probes and sequence the target nucleic acids.

Response to Arguments

The response traverses the rejection asserting that the claims require the staggered probe design of page 35. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not require a staggered probe design, but "wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." The teachings of Akhras teach two probes that do not overlap and target two sequences on the Neisseria gonorrhoeae chromosome.

Double Patenting

7. 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.

8. Claims 1, 3-4 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 13934093 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because coextensive in scope.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Instant claim 1 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe, and 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 the hybridized probes into a plurality of closed circularized

probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid..

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Claim 1 of '093 requires A method of analyzing a human nucleic acid for carrier screening, the method comprising:providing a sample from a human, the sample comprising human nucleic acid comprising a target nucleic acid; introducing a plurality of molecular inversion probes to the sample, wherein each of the plurality of molecular

inversion probes is defined by one of SEQ ID NOS: 185 through 3,254 hybridizing at least a portion of the molecular inversion probes to a plurality of sub- regions of the target nucleic acid,; converting the hybridized probes into covalently-closed circularized probes; isolating a plurality of circularized probes, each circularized probe containing a captured sub-region comprising a copy of one of the sub-regions; amplifying the circularized probes; sequencing the captured sub-regions; and analyzing the sequence to detect a mutation, thereby determining whether the human is a carrier of a disease..

The SEQ ID NO are to different genes and thus are consistent in scope with the claimed genes.

The dependent claims are merely obvious variant of the independent claims and obvious over the art of record.

Thus the claims render the instant claims obvious as they are a species of the instant claims.

Response to Arguments

The response request the provisional rejection be held in abeyance.

9. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No. 9,115,387. This is a statutory double patenting rejection.

Instant claim 1 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe, and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id.

However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Claim 1 of 387 requires, "A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; fragmenting the nucleic acid template to produce a plurality of fragments; tiling a plurality of molecular inversion probes across a portion of at least one of the fragments, wherein immediately adjacent probes hybridize to opposite strands of the at least one fragment and probes on the same strand hybridize to the at least one fragment in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the at least one fragment, thereby obtaining sequence information about the nucleic acid template"

Claim 2 of 387requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the

probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response provides no arguments to the instant rejection and thus appears to acquiesce on the rejection.

10. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No. 8,778,609. This is a statutory double patenting rejection.

Instant claim 1 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe, and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid.

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Claim 1 of 609 requires, "1. A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template

and probes on the same strand hybridize to the template in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template."

Claim 2 of 609 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

This is a new grounds of rejection.

11. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No. 9,677,124. This is a statutory double patenting rejection.

Instant claim 1 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe, and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Claim 1 of 124 requires, "1 A method for identifying an allelic status of a subject, the method comprising: obtaining a sample comprising a nucleic acid template from a subject; tiling a plurality of molecular inversion probes across both alleles of a locus on the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner; filling in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; analyzing the filled-in region of a plurality of the probes to obtain sequence information about both alleles of the locus; and identifying an allelic status based on the sequence information.."

Claim 2 of 124 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

This is a new grounds of rejection.

12. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No from allowed application 15/620129. This is a statutory double patenting rejection.

Instant claim 1 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; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the

target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe, and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a

method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

The independent claim 1 of 129 requires, "A method for reducing and/or detecting bias associated with capture, amplification and sequencing of nucleic acid, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner, and wherein each molecular inversion probe comprises a unique differentiator tag sequence; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template, wherein the sequence information comprises the differentiator tag sequences; identifying bias based on the sequence information."

Dependent claim requires, "The method according to claim 16, wherein analyzing is by sequencing."

Dependent claim 22 requires, "The method according to claim 21, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the

probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

This is a new grounds of rejection.

Summary

No claims are allowed.

Wang (Nucleic Acids Research (2005) volume 33, e183) is a reference of interest of MIPs for examination of SNPs in a target sequence.

Conclusion

13. 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. 13/266,862	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					
	B					
	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	Wang (Nucleic Acids Research (2005) volume 33, e183)
	V	Akhras (PLOS one (2007) volume 2(9) e915 and suppleental table)
	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., EX1002, p. 1600

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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)	2018-07-11
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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Petitioner Illumina, Inc., EX1002, p. 1602

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Application Number	13266862
Filing Date	2012-03-13
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	GSGE-002/01US 29258/20

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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)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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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-002/01US 29258/20

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	GSGE-002/01US 29258/20

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Examiner Signature	/Steven Pohnert/ (10/05/2018)	Date Considered	10/05/2018

*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:	34526894
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	12-DEC-2018
Filing Date:	13-MAR-2012
Time Stamp:	15:31:34
Application Type:	U.S. National Stage under 35 USC 371

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-002-01US-373_Statement.pdf	22203 93eea665e20156f495407630dde57488846d6d49	no	1
Warnings:					
Information:					
3	Application Data Sheet	MLB-002-01US_Updated-ADS.pdf	25566 eac3dda55243bb495a4464dad72fe88bb0dabf7e	no	6
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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.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.
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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)
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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.**

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

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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.
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Molecular Loop Biosolutions, LLC

Application No./Patent No.: 13/266,862 Filed/Issue Date: March 13, 2012

Titled: METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Molecular Loop Biosolutions, LLC (Name of Assignee) , a Limited Liability Company (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above, by virtue of either:

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 a copy* is attached.

OR

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: Inventors To: Good Start Genetics, Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 027860 , Frame 0025 , or a copy* is attached.

2. 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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[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[X] *As required by 37 CFR 3.73(b)(1)(i), if a copy/copies is/are attached, 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.]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Thomas C. Meyers/ — Signature
December 12, 2018 — Date

Thomas C. Meyers — Printed or Typed Name
36,989 — Title or Registration Number

63221739 v1

Supplemental Application Data Sheet

Application Information

Application number::	13/266,862
Filing Date::	03/13/12
Application Type::	Regular
Subject Matter::	Utility
Suggested classification::	435/006.100
Suggested Group Art Unit::	1634
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-002/01US 29258/20~~ MLB-002/01US 34468/8
Request for Early Publication?::	No
Request for Non-Publication?::	No
Small Entity?::	Yes
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

Applicant Information

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Petitioner Illumina, Inc., EX1002, p. 1640

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Representative Information

Representative Customer Number::	21710

Petitioner Illumina, Inc., EX1002, p. 1643

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::	Prior Appl Status::
This Application	a 371 of international	PCT/US10/01293	04/30/10	
PCT/US10/01293	Claims benefit of provisional	61/182089	05/28/09	Expired
PCT/US10/01293	Claims benefit of provisional	61/179358	05/18/09	Expired
PCT/US10/01293	Claims benefit of provisional	61/178923	05/15/09	Expired
PCT/US10/01293	Claims benefit of provisional	61/174470	04/30/09	Expired

Foreign Priority Information

Assignee Information

Assignee 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., EX1002, p. 1644

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.			
Signature	/Thomas C. Meyers/	Date	December 12, 2018
Name	Thomas C. Meyers	Registration No.	36,989

63213991 v1

Petitioner Illumina, Inc., EX1002, p. 1645

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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
13/266,862	03/13/2012	1634	1540	MLB-002/01US 34468/8	39	3

CONFIRMATION NO. 6082

CORRECTED FILING RECEIPT

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

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Date Mailed: 12/14/2018

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;
Jin Billy Li, Medford, MA;
E. Robert Wassman, Marblehead, MA;

Applicant(s)

Gregory Porreca, Cambridge, MA;
Uri Laserson, Boston, MA;
Jin Billy Li, Medford, MA;
E. Robert Wassman, Marblehead, MA;

Assignment For Published Patent Application

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 371 of PCT/US10/01293 04/30/2010
which claims benefit of 61/174,470 04/30/2009
and claims benefit of 61/174,923 05/01/2009
and claims benefit of 61/179,358 05/18/2009
and claims benefit of 61/182,089 05/28/2009

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.

Petitioner Illumina, Inc., EX1002, p. 1646

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/266,862**

Projected Publication Date: Not Applicable

Non-Publication Request: No

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:

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.

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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.

Petitioner Illumina, Inc., EX1002, p. 1647

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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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).

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Petitioner Illumina, Inc., EX1002, p. 1649

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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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
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8

CONFIRMATION NO. 6082

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

POA ACCEPTANCE LETTER

OC000000104463531

Date Mailed: 12/14/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/12/2018.

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**.

/sleutchit/

Electronic Acknowledgement Receipt

EFS ID:	34804736
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	09-JAN-2019
Filing Date:	13-MAR-2012
Time Stamp:	15:11:39
Application Type:	U.S. National Stage under 35 USC 371

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-002-01US_Response-01092019.pdf	128262 d091900cead4b519a2bd2eab098c9ad44b19b9c3	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	7
Warnings:			
Information:			
	Total Files Size (in bytes):	128262	

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-002/01US 34468/8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
APPL. NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	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 October 11, 2018, from the United States Patent and Trademark Office. A Terminal Disclaimer and requisite fee are filed herewith. Applicant believes no additional fees are due with this paper. Nevertheless, if any fee is required, Applicant authorizes the Commissioner to charge such fee to Deposit Account No. 50-0369.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

Amendments to the Claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently Amended) 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 is staggered with respect to hybridization regions flanking the target nucleic acid, and each different molecular inversion probe comprising: a 5' region comprising a 5' terminal nucleotide; a 3' region comprising a 3' terminal nucleotide; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe; and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid;

isolating the plurality of circularized probes; and

analyzing the target nucleic acid.

2. (Canceled)

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3. (Original) 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. (Original) 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.

5-67. (Canceled)

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Remarks

Claims 1, 3, and 4 are pending in the application. Claims 12-16, 20-30, 33, 36-38, 40-47, and 50-56 were previously withdrawn and are presently canceled. Claims 2, 5-11, 17-19, 31, 32, 34, 35, 38, 39, 48, 49, and 57-67 were previously canceled.

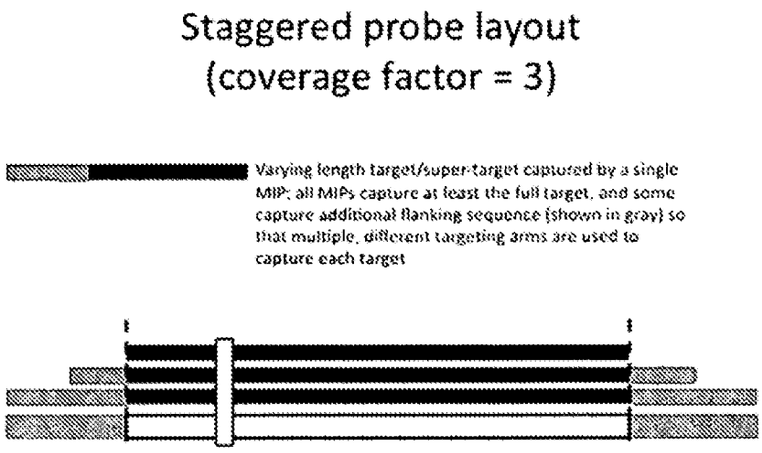
Claim 1 is currently amended. Claim 1 is amended to clarify the staggering probe design. Support for the amendment is found in the published application at paragraphs [0120], [0121] and [0124]. No new matter is added.

Rejections under 35 U.S.C. §102

The Office Action states at page 4 that claims 1, 3, and 4 are rejected under 35 U.S.C. §102(b) as being anticipated by Akhras (PLOS one, 2007, 2(9):e915 and supplemental table). Applicant respectfully submits that Akhras does not anticipate the amended claims.

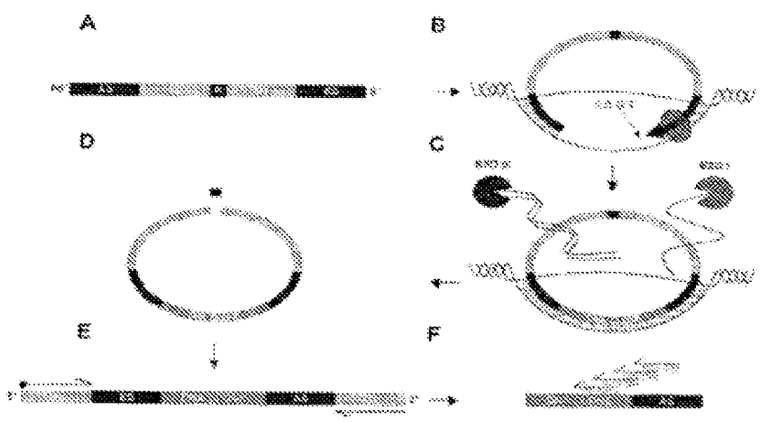
A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Akhras does not disclose a plurality of molecular inversion probes that are staggered with respect to hybridization regions flanking the target nucleic acid.

The claims require molecular inversion probes that are complimentary to nucleic acid residues flanking a target nucleic acid and having complimentary regions of different probes that do not overlap with each other and are staggered with respect to hybridization regions flanking the target nucleic acid. Each probe captures the full target nucleic acid and, in some cases, additional extra-target sequence. The resulting circularized probes contain the entire target nucleic acid. This "staggered probe layout" embodiment is shown in FIG. 2 of the application, reproduced below.



As recited in amended claim 1, a probe set comprises a plurality of different molecular inversion probes and each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid. This approach "staggers" the exact positions of the hybridization regions (i.e., the 5' region and the 3' region) flanking the target, which allows the MIPs to capture the full target with multiple probes having different targeting arms. *Published application, paragraph [0121].* Since the MIPs in the set are different, this variability in targeting arms solves problems associated with inefficient probe hybridization. *Published application, paragraph [0120].*

Akhras does not disclose the presently claimed staggered probe layout. As shown below in FIG. 1, Akhras is directed to an oligonucleotide probe containing 3' and 5' regions that bind to regions flanking a target, and then circularize to enrich the target DNA.



Though Akhras shows probes with binding regions that flank and capture a target sequence, Akhras fails to disclose a plurality of probes in a staggered approach. Akhras does not disclose probes that have complimentary regions that do not overlap with the complimentary regions of other probes. Akhras does not disclose that each probe in the probe set is staggered with respect to positions of the hybridization regions flanking the target nucleic acid. Thus, Akhras does not achieve a staggered probe layout for capturing the entire target.

Since Akhras does not disclose at least one element independent claim 1, Applicant submits that claim 1 is not anticipated by Akhras. Claims 3 and 4 depend from claim 1 and are not anticipated Akhras for at least the same reasons as claim 1. Therefore, Applicant requests that the 35 U.S.C. §102 rejection be withdrawn.

Nonstatutory Double Patenting Rejection

At page 9, the Office Action states that claims 1, 3, and 4 are rejected for nonstatutory double patenting over claim 1 of Application No. 13/934,093.

A terminal disclaimer to Application No. 13/934,093 is filed herewith. Therefore, Applicant submits the nonstatutory double patenting rejection is overcome and requests withdrawal of the nonstatutory double patenting rejection.

Statutory Double Patenting Rejections

At pages 12, 16, 19, and 23, the Office Action states that claims 1, 3, and 4 are rejected for statutory double patenting over claims 1-15 of prior U.S. Patent No. 9,115,387; claims 1-15 of prior U.S. Patent No. 8,778,609; claims 1-15 of prior U.S. Patent No. 9,677,124; and claims 1-15 from allowed Application No. 15/620,129.

Applicant submits the amendments to the claims differentiate independent claim 1 and dependent claims 3 and 4 from any claims in U.S. Patent No. 9,115,387; U.S. Patent No. 8,778,609; U.S. Patent No. 9,677,124; and Application No. 15/620,129.

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Specifically, Applicant submits that claim 1 is amended to include the feature "each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid", which clarifies the staggered probe layout. The feature "each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid" in currently amended independent claim 1 is not disclosed in any claims from U.S. Patent No. 9,115,387; U.S. Patent No. 8,778,609; U.S. Patent No. 9,677,124; and Application No. 15/620,129. Therefore, the presently pending claims are not identical to any of the claims from U.S. Patent No. 9,115,387; U.S. Patent No. 8,778,609; U.S. Patent No. 9,677,124; and Application No. 15/620,129.

Applicant respectfully requests consideration of the statutory double patenting rejections in view of the claim amendment. Applicant believes that the claim amendment addresses and overcomes all grounds of statutory double patenting rejections.

Conclusion

Applicant respectfully submits that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: January 9, 2019

Respectfully submitted,
BROWN RUDNICK LLP

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Email: tmeyers@brownrudnick.com

63251631 v1

Electronic Acknowledgement Receipt	
EFS ID:	34804649
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	09-JAN-2019
Filing Date:	13-MAR-2012
Time Stamp:	15:09:42
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	011019INTEFSW00001565500369
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	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	34032 188d56c783ab8d5146e8d8ace0533bffff478f5c	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30376 a2d33594441ee5436ff5135e7cf60e9e5eea5bd2	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	64408		

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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.

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	13266862
Filing Date	13-Mar-2012
First Named Inventor	Gregory Porreca
Attorney Docket Number	MLB-002/01US 34468/8
Title of Invention	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
MOLECULAR LOOP BIOSOLUTIONS, LLC	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

13934093 filed on 07/02/2013

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○	I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicant claims the following fee status:

◉ Small Entity

○ Micro Entity

○ Regular Undiscounted

I hereby 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 or imprisonment, or both, under Section 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.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 36989

○ A sole inventor

○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

○ A joint inventor; all of whom are signing this request

Signature	/THOMAS C. MEYERS/
Name	THOMAS C. MEYERS

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	13266862
Filing Date:	13-Mar-2012
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-002/01US 34468/8

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	2814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 13266862

Filing Date: 13-Mar-2012

Applicant/Patent under Reexamination: Porreca

Electronic Terminal Disclaimer filed on January 9, 2019

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8	6082

21710 7590 02/15/2019

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
02/15/2019	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. 13/266,862	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 1/9/2019.

☐ 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) 1 and 3-4 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) 1 and 3-4 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 4/8/2013 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., EX1002, p. 1668

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. 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 1/9/2019.

Claims 1, 3-4, are pending.

Claims 2, 5-67 have been canceled.

Claims 1, 3-4 are being examined.

Claim 1 has been amended.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 7/11/2018 is being considered by the examiner.

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) 1, 3-4 is/are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by Akhras et al (PLOS one (2007) volume 2 (9) e915 and supplemental table) (IDS 3/28/2013).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a a a circle upon hybrization.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

Claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap.

Akhras teaches, "The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay [17], which includes: i) probe hybridization, single "G" base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by relinearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target (Figure 1B). The 39end of the probe,

which we call the Extension Site (ES), primes for polymerization, while the 59end serves as point of ligation and is referred to as the Anchor Site (AS) (Figure 1). With all four dNTPs present, the polymerase is capable of extending past the intended point of ligation, generating a false negative. To address this problem, probes were designed to have an annealing temperature of approximately 5 degrees higher for the AS than that of the ES. The AS therefore blocks DNA extension when using a polymerase deficient in strand displacement at an appropriate intermediate temperature (50uC). For enhanced sensitivity and specificity a vast variety of probe concentrations and thermoprofiles were explored. Probes used in the 10–100 fmol concentration range yielded the strongest signal. Higher cycle numbers and shorter annealing times created a more efficient thermoprofile. The CIPer method successfully genotyped 1 pg of plasmid DNA in the presence of 200 ng non-reacting human genomic DNA, without generating any false positives (Figure S1). Assay optimizations were based on genotyping of HPV plasmid 56, validated by either SYBR GREEN assay or agarose gel electrophoresis, followed by Pyrosequencing verification (see Results, The Conserved Sequence Primer Connector Inversion Probe (CSP-CIPer)).”

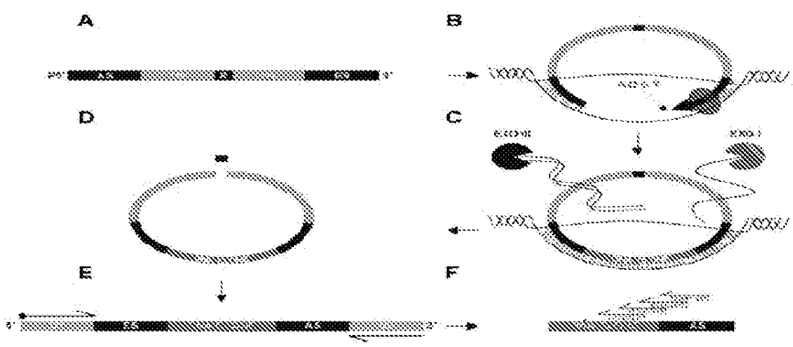


Figure 1. Schematic overview of Connector Inversion Probe (CIPer) technology. A) Synthetic oligonucleotide containing regions i) *AS and ES* (anchor site and extension sites; approximately 20 base pair fragments homologous to regions flanking target of interest, ii) *R*: restriction site for probe linearization, iii) *U1 and U2*: universal primer regions for inverted probe amplification. B) Target rescue through complete gap filling by a DNA polymerase and ligation-based probe circularization. C) Circular DNA enrichment through degradation of linear DNA by enzymes Exonuclease I and III, which are deactivated prior to the next step. D) Probe linearization by restriction site cleavage. E) Inverted probes are amplified with universal primers; one is biotinylated for subsequent amplicon validation. F) Amplicon validation using multiple sequencing primers.
doi:10.1371/journal.pone.0008915.g001

With regards to claims 1, 3 and 4, Akhras teaches, "CIPer detection was also applied to screening of resistance mutations in Neisseria gonorrhoeae. Two CIPers were used to perform a duplex amplification in a single-tube of the genes gyrA and parC [23], which are known to mutate easily and by specific SNPs generate resistance to ciprofloxacin and other quinolone antibiotics. The CIPers were designed with CIP creator 1.0.1 (http://bioel.stanford.edu/CIPer) based on previously described PCR primer-pairs not originally intended for multiplex PCR [21]. We intentionally inverted the gyrA CIPer to target the negative strand, while the parC CIPer targeted the positive strand, to illustrate that CIPers can be used on both DNA strands. In the case of close target proximities, it might be wise to revise such a strategy. Mutations on amino acid residues S91 and D95 for gyrA, and E91 for parC were the particular subjects of our interrogation. There are many other candidate genes for future CIPer-based epidemiological studies of antibiotic resistance [31]."

Thus CIPer probes to two different resistance mutations in two different Neisseria gonorrhoeae genes do not overlap in the 5' region and the 3' region (supplemental table).

Thus Akhras teaches providing a sample comprising a target nucleic acid (DNA clone), contacting the sample with a plurality of probes that flank to two different resistance mutations in two different Neisseria gonorrhoeae genes of the Neisseria gonorrhoeae chromosome do not overlap in the 5' region and the 3' region, converting the hybridized probe to a plurality of circularized probes comprising the target sequences, isolating the probes and sequence the target nucleic acids.

Response to Arguments

The response traverses the rejection asserting that the claims require the staggered probe design. While, claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition of staggered. In view of the guidance of the specification and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap. The teachings of Akhras teach two probes that do not overlap and target two sequences on the Neisseria gonorrhoeae chromosome.

Double Patenting

6. 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.

7. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No. 9,115,387. This is a statutory double patenting rejection.

Instant claim 1 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 is staggered with respect to hybridization regions flanking the target nucleic acid, and each different molecular inversion probe comprising: a 5' region comprising a 5' terminal nucleotide; a 3' region comprising a 3' terminal nucleotide; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion

probe; and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid."

Review of the specification provides support at 0121. The support does not provide any specific definition. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap.

Claim 1 of 387 requires, "A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; fragmenting the nucleic acid template to produce a plurality of fragments; tiling a plurality of molecular inversion probes across a portion of at least one of the fragments, wherein immediately adjacent probes hybridize to opposite strands of the at least one fragment and probes on the same strand hybridize to the at least one fragment in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the at least one fragment, thereby obtaining sequence information about the nucleic acid template"

Claim 2 of 387requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting that the claims require the staggered probe design. While, claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition of staggered. In view of the guidance of the specification and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap. The teachings of 387 teach two probes that do not overlap on the same strand.

8. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No. 8,778,609. This is a statutory double patenting rejection.

Instant claim 1 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 is staggered with respect to hybridization regions flanking the target nucleic acid, and each different molecular inversion probe comprising: a 5' region comprising a 5' terminal nucleotide; a 3' region comprising a 3' terminal nucleotide; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe; and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid..

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be

understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

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Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

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Claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap.

Claim 1 of 609 requires, "1. A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template."

Claim 2 of 609 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting that the claims require the staggered probe design. While, claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition of staggered. In view of the guidance of the specification and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap. The teachings of 387 teach two probes that do not overlap on the same strand.

9. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No. 9,677,124. This is a statutory double patenting rejection.

Instant claim 1 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 is staggered with respect to hybridization regions flanking the target nucleic acid, and each different molecular inversion probe comprising: a 5' region comprising a 5' terminal nucleotide; a 3' region comprising a 3' terminal nucleotide; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to

nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe; and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid..

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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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language, although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

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The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a

method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

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Claim 1 of 124 requires, "1 A method for identifying an allelic status of a subject, the method comprising: obtaining a sample comprising a nucleic acid template from a subject; tiling a plurality of molecular inversion probes across both alleles of a locus on the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner; filling in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; analyzing the filled-in region of a plurality of the probes to obtain sequence information about both alleles of the locus; and identifying an allelic status based on the sequence information.."

Claim 2 of 124 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting that the claims require the staggered probe design. While, claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition of staggered. In view of the guidance of the specification and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular

inversion probes that do not overlap. The teachings of 387 teach two probes that do not overlap on the same strand.

10. Claims 1, 3-4 is/are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1-15 of prior U.S. Patent No from allowed application 15/620129. This is a statutory double patenting rejection.

Instant claim 1 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 is staggered with respect to hybridization regions flanking the target nucleic acid, and each different molecular inversion probe comprising: a 5' region comprising a 5' terminal nucleotide; a 3' region comprising a 3' terminal nucleotide; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe; and 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 the hybridized probes into a plurality of closed circularized probes, each comprising the target nucleic acid; isolating the plurality of circularized probes; and analyzing the target nucleic acid.

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe that allows for formation of a circular probe upon hybridization to a target nucleic acid.

The specification does not teach a limiting definition of target nucleic acid or entire target nucleic acid. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

MPEP 2111 states: Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed, or by claim language that does not limit a claim to a particular structure. However, examples of claim language,

although not exhaustive, that may raise a question as to the limiting effect of the language in a claim are:

(A) "adapted to" or "adapted for" clauses;

(B) "wherein" clauses; and

(C) "whereby" clauses.

The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. See, e.g., Griffin v. Bertina, 283 F.3d 1029, 1034, 62 USPQ2d 1431 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps"). In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat'l Ass'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "'whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.'" Id.

Claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of

at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap.

The independent claim 1 of 129 requires, "A method for reducing and/or detecting bias associated with capture, amplification and sequencing of nucleic acid, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner, and wherein each molecular inversion probe comprises a unique differentiator tag sequence; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template, wherein the sequence information comprises the differentiator tag sequences; identifying bias based on the sequence information."

Dependent claim requires, "The method according to claim 16, wherein analyzing is by sequencing."

Dependent claim 22 requires, "The method according to claim 21, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the

probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting that the claims require the staggered probe design. While, claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition of staggered. In view of the guidance of the specification and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap. The teachings of 387 teach two probes that do not overlap on the same strand.

Summary

No claims are allowed.

Conclusion

11. **THIS ACTION IS MADE FINAL.** 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.

12. 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.

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

Electronic Acknowledgement Receipt	
EFS ID:	36013571
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Annie Kock
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/01US 34468/8
Receipt Date:	14-MAY-2019
Filing Date:	13-MAR-2012
Time Stamp:	19:08:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$950
RAM confirmation Number	051519INTEFSW00008211500369
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	Request for Continued Examination (RCE)	MLB-002-01US-RCE.pdf	2273814 7c48773588206299f4305870ded2ec64a12e39a6	no	3
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2		MLB-002-01US-Response-051419.pdf	31240 bb7281284fa9f84bb7418ea2e4bc0890be78c401	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	4	6
	Claims	2	3
	Amendment Submitted/Entered with Filing of CPA/RCE	1	1

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30682 03ffa55bab59756f4b5fe884bdd10d4979bf8042	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2335736		

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.

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	13/266,862	Filing Date	2012-03-13	Docket Number (if applicable)	MLB-002/01US 34468/8	Art Unit	1634
First Named Inventor	Gregory Porreca			Examiner Name	Steven 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 500369

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

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)	2019-05-14
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.

Attorney Docket No. MLB-002/01US 34468/8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTORS:	Porreca et al.	ART UNIT:	1634
APPL. NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

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

FILED ELECTRONICALLY

RESPONSE AND AMENDMENT SUBMITTED WITH REQUEST FOR CONTINUED EXAMINATION

This paper is in response to the final office action mailed February 15, 2019, from the United States Patent and Trademark Office.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

A Request for Continued Examination and requisite fees are submitted herewith. Applicant believes no other fees are due with this paper. Nevertheless, if any fees are required, Applicant authorizes the Commissioner to charge such fees to Deposit Account No. 50-0369.

Amendments to the Claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently Amended) 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, ~~different molecular inversion probe is~~

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 ~~with respect to hybridization regions flanking the target nucleic acid, and each different molecular inversion probe comprising: a 5' region comprising a 5' terminal nucleotide; a 3' region comprising a 3' terminal nucleotide; and a central region flanked by the 5' region and the 3' region; wherein the 5' region is complementary to nucleic acid residues flanking a 3' end of the target nucleic acid and the 3' region is complementary to nucleic acid residues flanking a 5' end of the target nucleic acid; wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe; and 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 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

analyzing the target nucleic acid.

2. (Canceled)

3. (Currently Amended) The method of claim 1, wherein the sequences of the 5' targeting arm ~~region~~ and the 3' targeting arm ~~region~~ of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm ~~region~~ and the 3' targeting arm ~~region~~ of each other probe.

4. (Currently Amended) The method of claim 1, wherein the sequences of the 5' targeting arm ~~region~~ and the 3' targeting arm ~~region~~ of each probe are, respectively, different than the sequences of the 5' targeting arm ~~region~~ and the 3' targeting arm ~~region~~ of each other probe.

5-67. (Canceled)

68. (New) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized to the target nucleic acid, are separated by a plurality of nucleotides on the target nucleic acid.

Petitioner Illumina, Inc., EX1002, p. 1705

Remarks

Claims 1, 3, 4, and 68 are pending in the application. Claim 68 is newly added. Claims 2 and 5-67 were previously canceled. Claims 1, 3, and 4 are currently amended. The amendments are directed to the staggered probe layout, and support is found pages 34, lines 30-32; page 35, lines 1-15 and 24-31; and FIG. 2 of the as-filed application. Support for new claim 68 is found at page 12, lines 10-24; page 60, line 28, to page 62, line 22; page 74, line 30, to page 75, line 17; and FIG. 9 of the as-filed application. No new matter is added.

Rejections under 35 U.S.C. §102

The Office Action states at page 4 that claims 1, 3, and 4 are rejected under 35 U.S.C. §102(b) as being anticipated by Akhras (PLOS one, 2007, 2(9):e915 and supplemental table). Applicant respectfully submits that Akhras does not anticipate 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. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Akhras does not disclose a plurality of molecular inversion probes that have a staggered layout.

As amended, claim 1 is directed to a staggered probe layout in which a plurality of molecular inversion probes (MIPs), each having two targeting arms, hybridize upstream and downstream of a target in the target nucleic acid. The MIPs are provided in a staggered layout on each target such that all of the molecular inversion probes (MIPs) capture the target, and some MIPs in the probe set capture additional flanking sequence.

Akhras does not disclose or suggest a staggered probe layout. Akhras reports an oligonucleotide probe containing 3' and 5' regions that bind to regions flanking a target, and then are circularized to enrich the target DNA. *Akhras, FIG. 1 and related description.* Akhras reports probes that capture only a target sequence and makes no reference to a staggered probe layout of MIPs that can capture additional flanking sequence in addition to the target. Akhras' failure to

disclose staggered probes renders its disclosure inoperative for the detection of flanking sequence as required in the present claims.

Since Akhras does not disclose an element of amended claim 1, amended claim 1 is not anticipated by Akhras. Claims 3 and 4 (and new claim 68) depend from claim 1 and are not anticipated by Akhras for at least the same reasons as claim 1. Therefore, Applicant requests that the 35 U.S.C. §102 rejection be withdrawn.

Statutory Double Patenting Rejections

At pages 9, 14, 18, and 23, the Office Action states that claims 1, 3, and 4 are rejected for statutory double patenting over claims 1-15 of prior U.S. Patent No. 9,115,387; claims 1-15 of prior U.S. Patent No. 8,778,609; claims 1-15 of prior U.S. Patent No. 9,677,124; and claims 1-15 from allowed Application No. 15/620,129.

Applicant submits the amendments to the claims differentiate independent claim 1 and dependent claims 3 and 4 from any claims in U.S. Patent No. 9,115,387; U.S. Patent No. 8,778,609; U.S. Patent No. 9,677,124; and Application No. 15/620,129. Applicant believes that the claim amendments address and overcome all grounds of statutory double patenting rejections.

Petitioner Illumina, Inc., EX1002, p. 1707

Conclusion

Applicant respectfully submits that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: May 14, 2019

Respectfully submitted,
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63399445 v1

Petitioner Illumina, Inc., EX1002, p. 1708

Electronic Patent Application Fee Transmittal	
Application Number:	13266862
Filing Date:	13-Mar-2012
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Annie Kock
Attorney Docket Number:	MLB-002/01US 34468/8
Filed as Small Entity	
Filing Fees for U.S. National Stage under 35 USC 371	

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:	36881691
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	15-AUG-2019
Filing Date:	13-MAR-2012
Time Stamp:	12:10:10
Application Type:	U.S. National Stage under 35 USC 371

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	Information Disclosure Statement (IDS) Form (SB08)	34468_8US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1034679 6702b9e1be2c30de8892aba4268617d58f29da9c	no	4

Warnings:

Information:					
2	Non Patent Literature	34468_8US_-_Akhras-2007-PLoSOne.PDF	212811 290afe15df59bce64f053e8d4059d06bb72159c8	no	6
Warnings:					
Information:					
3	Non Patent Literature	34468_8US_-_Thiyagarajan-2006-BMCBioinformatics.pdf	303991 462fcbf6682ae1796576dc1c0e1ed5190f4db44a	no	10
Warnings:					
Information:					
4	Non Patent Literature	Meyer-2008-NatProt.pdf	1111770 d48569c83ad17880320f76a8906b3957aca183b2	no	12
Warnings:					
Information:					
			Total Files Size (in bytes):	2663251	

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
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	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8US

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)	2019-08-15
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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13266862
Filing Date	2012-03-13
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	MLB-002/01US 34468/8US

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					

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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	20060008824	A1	2006-01-12	Ronaghi et al.	
	2	20060263789	A1	2006-11-23	Kincaid	

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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	13266862
	Filing Date	2012-03-13
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	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8US

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	Akhras, 2007, Connector inversion probe technology: A powerful one-primer multiplex DNA amplification system for numerous scientific applications, PLoSOne 9:e915	
	2	Meyer, 2008, Parallel tagged sequencing on the 454 platform, Nat Protocol 3(2):267-278	
	3	Thiyagarajan, 2006, PathogenMIPer: a tool for the design of molecular inversion probes to detect multiple pathogens, BMC Bioinformatics 7:500	

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.

Electronic Acknowledgement Receipt	
EFS ID:	37432262
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	11-OCT-2019
Filing Date:	13-MAR-2012
Time Stamp:	12:26:42
Application Type:	U.S. National Stage under 35 USC 371

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	34468_8US_-_Porreca-2007-NatMethpt1.pdf	22417770 0f4c340e6127a3f45fffab4b183fbd1910464b86	no	111

Warnings:

Information:					
2	Non Patent Literature	34468_8US_-_Porreca-2007-NatMethpt2.pdf	23112435 f02c29c2e241eb490aa06d6cc3e637c5b0ede747	no	111
Warnings:					
Information:					
3	Non Patent Literature	34468_8US_-_Porreca-2007-NatMethpt3.pdf	23126159 840389f8dedcaa33a6d1c8338e097787e8b291ac	no	111
Warnings:					
Information:					
4	Non Patent Literature	34468_8US_-_Porreca-2007-NatMethpt4.pdf	23012236 5a67c398a686f77f0ae72f76e80d4e8f1d7c81c8	no	111
Warnings:					
Information:					
5	Non Patent Literature	34468_8US_-_Porreca-2007-NatMethpt5.pdf	23263550 7ac669b7e92e9578ce6283f10f9899d63d117d21	no	113
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	34468_8US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1034430 524aff30af32d0af038bd696e72a9433f11147f3	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	115966580		

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.

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	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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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)	2019-10-11
Name/Print	Thomas C. Meyers	Registration Number	36,989

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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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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.

Petitioner Illumina, Inc., EX1002, p. 1721

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
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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	10227635		2019-03-12	Umbarger et al.	
	2	9115387		2015-08-25	Umbarger	
	3	9677124		2017-06-13	Umbarger	

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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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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	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							

EFS Web 2.1.18

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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NON-PATENT LITERATURE DOCUMENTS [Remove]

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	Porreca, 2007, Multiplex amplification of large sets of human exons, Nat Meth 1-557	

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.

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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.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8	6082

21710 7590 01/22/2020

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
01/22/2020	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.** 13/266,862	**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 5/14/2019.

☐ 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) 1,3-4 and 68 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) 1,3-4 and 68 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 4/8/2013 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.

Continued Examination Under 37 CFR 1.114

2. 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 5/14/2019 has been entered.

Claim Status and Formal matters

This action is in response to papers filed 5/14/2019.

Claims 1, 3-4, are pending.

Claims 2, 5-67 have been canceled.

Claim 68 has been added.

Claim 1 has been amended.

Claims 1, 3-4 and 68 are being examined.

The previous 102 rejection has been withdrawn in view of the amendment.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application

61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 8/15/2019 and 10/11/2019 is being considered by the examiner.

Claim Rejections - 35 USC § 103

4. 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.

5. Claim 1, 4, 68 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Akhras et al (PLOS one (2007) volume 2 (9) e915 and supplemental table) (IDS 3/28/2013) and Chee et al (WO 95/11995).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

The specification does not teach a limiting definition of target nucleic acid or target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

The specification provides no definition of staggering. The specification states on page 35 that a set of probes:

"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 MTPs used to capture aven molecule". In view of the guidance and art of record the amendment provides the probe

set are "staggered" by the broadest reasonable interpretation. This appears to be the obvious positioning of probes of a set or plurality of probes that allow for inclusion of additional flanking nucleotides for hybridization.

Akhras teaches, "The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay [17], which includes: i) probe hybridization, single "G" base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by relinearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target (Figure 1B). The 39end of the probe, which we call the Extension Site (ES), primes for polymerization, while the 59end serves as point of ligation and is referred to as the Anchor Site (AS) (Figure 1). With all four dNTPs present, the polymerase is capable of extending past the intended point of ligation, generating a false negative. To address this problem, probes were designed to have an annealing temperature of approximately 5 degrees higher for the AS than that of the ES. The AS therefore blocks DNA extension when using a polymerase deficient in strand displacement at an appropriate intermediate temperature (50uC). For enhanced sensitivity and specificity a vast variety of probe concentrations and thermoprofiles were explored. Probes used in the 10–100 fmol concentration range yielded the strongest signal. Higher cycle numbers and shorter annealing times created a more efficient thermoprofile. The CIPer method successfully genotyped 1 pg of plasmid DNA in the presence of 200 ng non-reacting human genomic DNA, without generating any false positives (Figure S1). Assay optimizations were based on

genotyping of HPV plasmid 56, validated by either SYBR GREEN assay or agarose gel electrophoresis, followed by Pyrosequencing verification (see Results, The Conserved Sequence Primer Connector Inversion Probe (CSP-CIPer))."

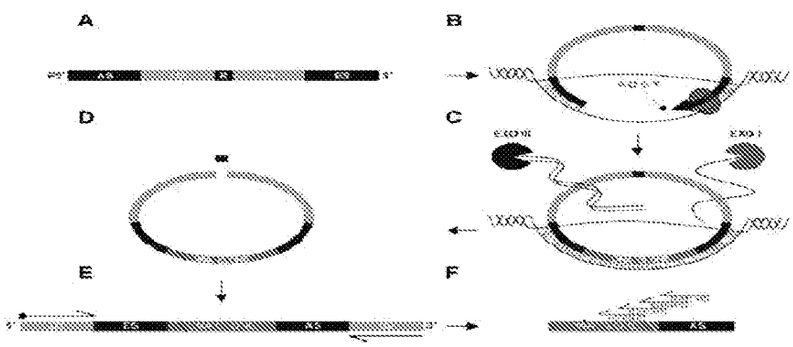


Figure 1. Schematic overview of Connector Inversion Probe (CIPer) technology. A) Synthetic oligonucleotide containing regions i) *AS and ES* (anchor site and extension site): approximately 20 base pair fragments homologous to regions flanking target of interest, ii) *R*: restriction site for probe linearization, iii) *U1 and U2*: universal primer regions for inverted probe amplification. B) Target rescue through complete gap filling by a DNA polymerase and ligation-based probe circularization. C) Circular DNA enrichment through degradation of linear DNA by enzymes Exonuclease I and III, which are deactivated prior to the next step. D) Probe linearization by restriction site cleavage. E) Inverted probes are amplified with universal primers; one is biotinylated for subsequent amplicon validation. F) Amplicon validation using multiple sequencing primers.
doi:10.1371/journal.pone.0009915.g001

With regards to claims 1, 4, 68, Akhras teaches, "CIPer detection was also applied to screening of resistance mutations in Neisseria gonorrhoeae. Two CIPers were used to perform a duplex amplification in a single-tube of the genes gyrA and parC [23], which are known to mutate easily and by specific SNPs generate resistance to ciprofloxacin and other quinolone antibiotics. The CIPers were designed with CIP creator 1.0.1 (http://bioel.stanford.edu/CIPer) based on previously described PCR primer-pairs not originally intended for multiplex PCR [21]. We intentionally inverted the gyrA CIPer to target the negative strand, while the parC CIPer targeted the positive strand, to illustrate that CIPers can be used on both DNA strands. In the case of close target proximities, it might be wise to revise such a strategy. Mutations on amino acid residues S91 and D95 for gyrA, and E91 for parC were the particular subjects of our

interrogation. There are many other candidate genes for future CIPer-based epidemiological studies of antibiotic resistance [31]."

Thus Akhras teaches providing a sample comprising a target nucleic acid (DNA clone), contacting the sample with a plurality of probes that flank two different resistance mutations in two different Neisseria gonorrhoeae genes of the Neisseria gonorrhoeae chromosome that do not overlap in the 5' region and the 3' region, converting the hybridized probe to a plurality of circularized probes comprising the target sequences, isolating the probes and sequence the target nucleic acids.

Arkhas does not specifically teach MIP probe sets which allow for additional flanking nucleotides to be hybridized.

However, Chee et al teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an array of capture probes (see figure 16,and page 79 lines 23-39) exemplified by using a block tiling arrays to determine nucleic acid sequences of chosen sites and adjacent bases (see Figure7 and page 37 line 10- page 38 line 34).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use MIPS with suitable arrays such as block tiling arrays. The artisan would be motivated to detect mutations near known SNPs or

nucleotides of interest, as exemplified by Chee. In addition, one of ordinary skill in the art would have been motivated to employ overlapping and/or staggered probe sets/arrays in addition to or as a substitution of titling arrays in the meth9od of Arkhas. One of ordinary skill in the art would have motivated to employed obvious patterning variants as a matter of design choice in order to enhance suitable captures of flanking residues of target hybridization sites, as suggested by Chee. The artisan would have a reasonable expectation of success as the artisan is merely using known methods or strategies of designing MIPS to analyze known sequences.

Response to Arguments

This is a new ground of rejection

6. Claim 1, 3-4, 68 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Bhangale (Nature genetics (2006) volume 38, pages 1457-1462), Hardenbohl (Nature Biotechnology (2003) volume 21, pages 673-678) and Akhras et al (PLOS one (2007) volume 2 (9) e915 and supplemental table) (IDS 3/28/2013).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

The specification does not teach a limiting definition of target nucleic acid or target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

The specification provides no definition of staggering. The specification states on page 35 that a set of probes:

"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") bv changing the number of different MTPs used to capture aven molecule". In view of the guidance and art of record the amendment provides the probe

set are "staggered" by the broadest reasonable interpretation. This appears to be the obvious positioning of probes of a set or plurality of probes that allow for inclusion of additional flanking nucleotides for hybridization.

Bhangale teaches, " The development of high-density genetic maps across the human genome provides unparalleled resources for analyzing the association between common sequence polymorphism and common disease18. Once applied, these resources are likely to identify the region(s) associated with specific phenotype(s), and subsequent studies will turn to completely cataloguing the variation in the region of interest for specific populations or individuals to identify variants for further molecular analysis. Resequencing has been the gold standard in polymorphism discovery, and with its rapid increase in throughput and reduction in costs, it is expected to remain at the forefront for variant identification. One in every 15 diallelic sites is an indel (Table 1). Aside from their value in increasing the resolution of genetic maps, indel polymorphisms can also have an important role as functional variants" (page 1459).

Thus Bhangale teaches the use of SNPs to identify regions associated with a phenotype. Bhangale further suggests examining mutations in the region encompassing the SNP.

Bhangle does not specifically teach use of MIPs to detect SNPs or regions encompassing SNPs.

However, Hardenbohl teaches methods of detecting SNPs by use of MIPs (title, page 647 molecular inversion probe genotyping).

Akhras teaches, "The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip

assay [17], which includes: i) probe hybridization, single "G" base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by relinearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target (Figure 1B). The 39end of the probe, which we call the Extension Site (ES), primes for polymerization, while the 59end serves as point of ligation and is referred to as the Anchor Site (AS) (Figure 1). With all four dNTPs present, the polymerase is capable of extending past the intended point of ligation, generating a false negative. To address this problem, probes were designed to have an annealing temperature of approximately 5 degrees higher for the AS than that of the ES. The AS therefore blocks DNA extension when using a polymerase deficient in strand displacement at an appropriate intermediate temperature (50uC). For enhanced sensitivity and specificity a vast variety of probe concentrations and thermoprofiles were explored. Probes used in the 10–100 fmol concentration range yielded the strongest signal. Higher cycle numbers and shorter annealing times created a more efficient thermoprofile. The CIPer method successfully genotyped 1 pg of plasmid DNA in the presence of 200 ng non-reacting human genomic DNA, without generating any false positives (Figure S1). Assay optimizations were based on genotyping of HPV plasmid 56, validated by either SYBR GREEN assay or agarose gel electrophoresis, followed by Pyrosequencing verification (see Results, The Conserved Sequence Primer Connector Inversion Probe (CSP-CIPer))."

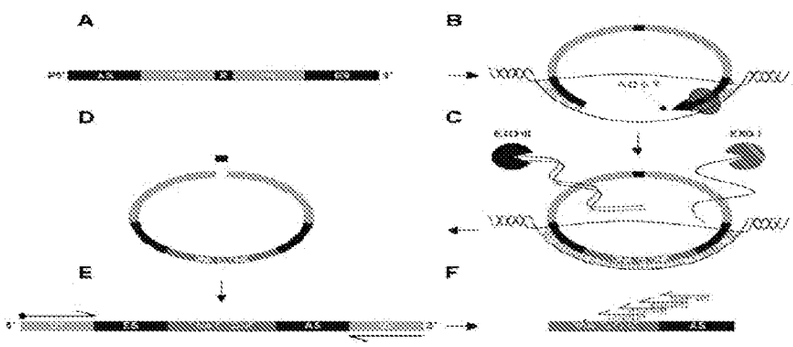


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doi:10.1371/journal.pone.0008915.g001

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention to design probes to detect a SNP (MIP) and regions encompassing the in the middle SNP (CIP) in patterns suitable for capturing more nucleotides adjacent to target sites. The artisan would be motivated to identify SNPs indicative of a phenotype with the ability to examine a larger region encompassing the SNP to identify the presence or absence of additional SNPs or insertion/deletions in the area. The artisan would have a reasonable expectation of success.

With regards to claim 3-4, 68, the CIP for encompassing the SNP in context of a region render obvious probes that are non-overlapping 5' and 3' target arms as Akhras suggests DNA targeted is approximately 100 nucleotides while the SNP probes of Hardenbohl teaches targeting arms of 6 nucleotides on either side of the SNP (figure 2b).

Response to Arguments

This is a new grounds of rejection

Double Patenting

7. 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.

8. Claims 1, 4 , 68 rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 9,115,387.

The instant independent claim 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, different 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 analyzing the target nucleic acid.

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in

an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

The specification does not teach a limiting definition of target nucleic acid or target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

The specification provides no definition of staggering. The specification recites, "staggering/tiling" and thus suggest they are the same or obvious variants. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be anything that allows for inclusion of additional flanking nucleotides. Claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121.

The support does not provide any specific definition. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap.

Claim 1 of 387 requires, "A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; fragmenting the nucleic acid template to produce a plurality of fragments; tiling a plurality of molecular inversion probes across a portion of at least one of the fragments, wherein immediately adjacent probes hybridize to opposite strands of the at least one fragment and probes on the same strand hybridize to the at least one fragment in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the at least one fragment, thereby obtaining sequence information about the nucleic acid template"

Claim 2 of 387requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting amendment has overcome the rejection. This argument is not persuasive for the reasons detailed in the rejection.

9. Claims 1, 3-4 and 68 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 8,778,609. This is a nonstatutory double patenting rejection.

The instant independent claim 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, different 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 analyzing the target nucleic acid.

MPEP 2111 states:

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MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

The specification does not teach a limiting definition of target nucleic acid or target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

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guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be anything that allows for inclusion of additional flanking nucleotides. Claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121. The support does not provide any specific definition. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap.

Claim 1 of 609 requires, "1. A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template."

Claim 2 of 609 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting amendment has overcome the rejection. This argument is not persuasive for the reasons detailed in the rejection.

10. Claims 1, 3-4 and 68 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 9,677,124. This is a nonstatutory double patenting rejection.

The instant independent claim 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, different 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 analyzing the target nucleic acid.

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> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

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> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

The specification does not teach a limiting definition of target nucleic acid or target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

The specification provides no definition of staggering. The specification recites, "staggering/tiling" and thus suggest they are the same or obvious variants. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be anything that allows for inclusion of additional flanking nucleotides.

Claim 1 of 124 requires, "a method for identifying an allelic status of a subject, the method comprising: obtaining a sample comprising a nucleic acid template from a subject; tiling a plurality of molecular inversion probes across both alleles of a locus on the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner; filling in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; analyzing the filled-in region of a plurality of the probes to obtain sequence information about both alleles of the locus; and identifying an allelic status based on the sequence information.."

Claim 2 of 124 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the

probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting amendment has overcome the rejection. This argument is not persuasive for the reasons detailed in the rejection.

11. Claims 1, 3-4 and 68 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 16-30 of U.S. Patent 10202637 No from allowed application 15/620129. This is a nonstatutory double patenting rejection.

The instant independent claim 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, different 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 analyzing the target nucleic acid.

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in

an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

The specification does not teach a limiting definition of target nucleic acid or target. However the specification states, "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)." Thus, the broadest reasonable interpretation of a target nucleic acid is a two nucleotides.

The specification provides no definition of staggering. The specification recites, "staggering/tiling" and thus suggest they are the same or obvious variants. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be anything that allows for inclusion of additional flanking nucleotides. Claim 1 has been amended to recite," each different molecular inversion probe is staggered with respect to hybridization regions flanking the target nucleic acid." Review of the specification provides support at 0121.

The support does not provide any specific definition. In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be description of wherein clause of " wherein the 5' region and the 3' region of at least one of the molecular inversion probes do not overlap with the 5' region and 3' region of at least one other molecular inversion probe." Thus the broadest reasonable interpretation is molecular inversion probes that do not overlap.

The independent claim 16 of 129 requires, "A method for reducing and/or detecting bias associated with capture, amplification and sequencing of nucleic acid, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner, and wherein each molecular inversion probe comprises a unique differentiator tag sequence; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template, wherein the sequence information comprises the differentiator tag sequences; identifying bias based on the sequence information.."

Dependent claim 17 requires, "The method according to claim 16, wherein analyzing is by sequencing."

Dependent claim 22 requires, "The method according to claim 21, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism

(SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting amendment has overcome the rejection. This argument is not persuasive for the reasons detailed in the rejection.

Summary

No claims are allowed.

Conclusion

12. 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. 13/266,862	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					
	B					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N	WO-9511995-A1	05-1995	WO	CHEE	C12Q1/6837
	O					
	P					
	Q					
	R					
	S					
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NON-PATENT DOCUMENTS

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	U	Bhangale (Nature genetics (2006) volume 38, pages 1457-1462),
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Petitioner Illumina, Inc., EX1002, p. 1752

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

CERTIFICATION STATEMENT

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

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OR

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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)	2019-10-11
Name/Print	Thomas C. Meyers	Registration Number	36,989

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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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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.

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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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13266862
Filing Date	2012-03-13
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	MLB-002/01US 34468/8

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/SP/	1	10227635		2019-03-12	Umbarger et al.	
/SP/	2	9115387		2015-08-25	Umbarger	
/SP/	3	9677124		2017-06-13	Umbarger	

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/SP/	1	Porreca, 2007, Multiplex amplification of large sets of human exons, Nat Meth 1-557	

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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)	2019-08-15
Name/Print	Thomas C. Meyers	Registration Number	36,989

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

PTO/SB/08a (02-18)
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First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	MLB-002/01US 34468/8US

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/SP/	1	20060008824	A1	2006-01-12	Ronaghi et al.	
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	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8US

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/SP/	1	Akhras, 2007, Connector inversion probe technology: A powerful one-primer multiplex DNA amplification system for numerous scientific applications, PLoSOne 9:e915	
/SP/	2	Meyer, 2008, Parallel tagged sequencing on the 454 platform, Nat Protocol 3(2):267-278	
/SP/	3	Thiyagarajan, 2006, PathogenMIPer: a tool for the design of molecular inversion probes to detect multiple pathogens, BMC Bioinformatics 7:500	

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EFS ID:	38427675
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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
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Attorney Docket Number:	MLB-002/01US 34468/8
Receipt Date:	05-FEB-2020
Filing Date:	13-MAR-2012
Time Stamp:	15:50:34
Application Type:	U.S. National Stage under 35 USC 371

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1	Non Patent Literature	Li-2003-EMBOJ.pdf	560612 9f67fffae4b8643ec7174a7d2ddbfc3d0849d6be	no	12
Warnings:					
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2	Foreign Reference	WO2011066476A1.pdf	5302814 286fa76cdf2faf9bc9484b68be087b8ea451f1d8	no	77
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Information:					
3	Foreign Reference	WO2011067378A1.pdf	1915901 60c3eb2dd2e67ad5b7b27d785d2de9266ff89578	no	36
Warnings:					
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4	Foreign Reference	34468_30US_-_WO2007061284A1.pdf	1193373 75b6280e3fad2a783631375d7abc1bfae9059ae8	no	76
Warnings:					
Information:					
5	Non Patent Literature	34468_30US_-_Wahl-1979-PNAS.pdf	1446306 1948e732454e8e31fe6988253942fd1402931777	no	5
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	MLB-002-01US_IDS.pdf	1035158 f3a08021d1ab5037be13b3a10de61e290c63cc63	no	5
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7	Fee Worksheet (SB06)	fee-info.pdf	30347 240fd9f2cf973d9e39aad00e04377808a9a88aec	no	2
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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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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)	2020-02-05
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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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
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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	1	20140228226	A1	2014-08-14	Yin et al.	
	2	20110288780	A1	2011-11-24	Rabinowitz et al.	
	3	20120270739	A1	2012-10-25	RAVA et al.	
	4	20150051085	A1	2015-02-19	Vogelstein et al.	
	5	20170044610	A1	2017-02-16	Johnson	

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	First Named Inventor	Gregory Porreca
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	Attorney Docket Number	MLB-002/01US 34468/8

	6	20140342354	A1	2014-11-20	Evans et al.	
	7	20040121373	A1	2004-06-24	Friedlander et al.	
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	1	2011066476	WO	A1	2011-06-03	Quantalife, Inc		
	2	2011067378	WO	A1	2011-06-09	Olink Genomics Ab		
	3	2007/061284	WO	A1	2007-05-31	Plant Res Int BV		

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	1	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	

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	MLB-002/01US 34468/8

	2	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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[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 Patent Application Fee Transmittal	
Application Number:	13266862
Filing Date:	13-Mar-2012
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-002/01US 34468/8
Filed as Large Entity	
Filing Fees for U.S. National Stage under 35 USC 371	

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($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt	
EFS ID:	39214481
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	21-APR-2020
Filing Date:	13-MAR-2012
Time Stamp:	14:26:38
Application Type:	U.S. National Stage under 35 USC 371

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-002-01US-Response-200122.pdf	89813 18f21139076e641773e77831b552480c948f5280	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	11
Warnings:			
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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
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-002/01US 34468/8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
APPL. NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

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

FILED ELECTRONICALLY

RESPONSE

This paper is in response to the non-final Office Action mailed January 22, 2020, from the United States Patent and Trademark Office.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

If any fees are required, Applicant authorizes the Commissioner to charge such fees to Deposit Account No. 50-0369.

Amendments to the Claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently Amended) 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 at least 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

analyzing the target ~~nucleic acid~~.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

4. (Currently Amended) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, different than the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

Petitioner Illumina, Inc., EX1002, p. 1774

5-67. (Canceled)

68. (Currently Amended) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized to the target ~~nucleic acid~~, are separated by a plurality of nucleotides on the target ~~nucleic acid~~.

69. (New) The method of claim 1, wherein the target comprises at least 50 base pairs of DNA.

Petitioner Illumina, Inc., EX1002, p. 1775

Remarks

Claims 1, 3, 4, and 68-69 are pending in the application, with claim 1 being the only independent claim. Claims 1 and 68 are amended and claim 69 is new. Support for the claim amendment and the new claim can be found throughout the as-filed application, for example at pages 35-36 and Figure 2. No new matter is added.

Rejections under 35 U.S.C. §103

The Office Action, at page 3, states that claims 1, 4, and 68 are rejected under 35 U.S.C. §103 over Akhras, et al., (PLOS one, 2007, 2(9):e915 and supplemental table) and Chee, et al. (WO 95/11995). The Office Action, at page 8, states claims 1, 3-4, and 68 are rejected under 35 U.S.C. §103 over Bhangale, et al., (Nature genetics (2006) volume 38, pages 1457-1462), Hardenbohl, et al., (Nature Biotechnology (2003) volume 21, pages 673-678), and Akhras.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met 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. *See, In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In addition to the requirements for making a combination, an obviousness rejection cannot be established in the first place unless each claim element is disclosed in the cited art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Applicants submit that the Office has not established a *prima facie* case as required under the law because none of the cited art disclose molecular inversion probes in a staggered layout as required by the current claims.

The burden to make a *prima facie* case under Section 103 is on the Office. Applicants respectfully submit that it is not possible to meet the standard for a *prima facie* rejection when

not a single one of the references reports or suggest an element of the claims. For example, independent claim 1 recites a probe set having a staggered probe layout in which each of the plurality of molecular inversion probes (MIPs) of the probe set has two targeting arms that hybridize upstream and downstream of a target that includes at least the target.

Applicant submits that none of the cited references disclose a probe set comprising a plurality of MIPs having a staggered layout. Instead of providing a reference that shows that element, the Office Action, at pages 4-5, states that the specification provides no definition of staggering. That statement does not make up for the failure of the art to disclose an element of the claims. Moreover, Applicant submits that "staggering" and the associated "staggered layout" embodiment is clearly shown in Figure 2, described at pages 35-36 of the as-filed application, and defined in the present claims.

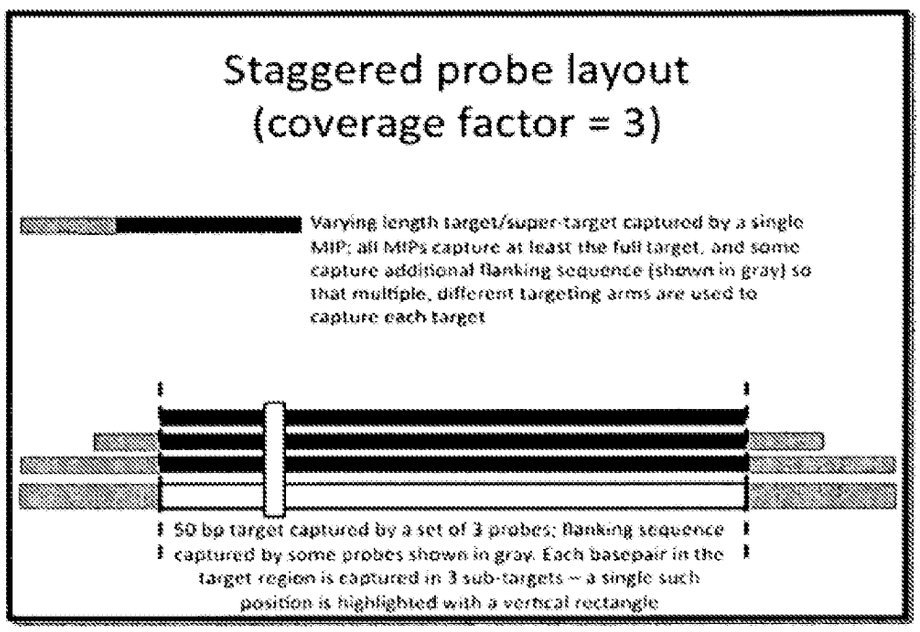
Staggering describes the differing (varying) target lengths the MIP set captures. Particularly, all of the MIPs capture at least the target nucleic acid of interest and each MIP captures a different number of additional base pairs on either end of the target, such that each MIP in the probe set has a target with a different length than a target length of other MIPs in "the set".

As described in the as-filed application, the probe set can be designed to 'stagger' the exact positions of the hybridization regions flanking the target nucleic acid, thereby capturing the full target nucleic acid of interest and in some cases, also capturing some additional flanking sequence. *As flied application, pg. 35 (lines 8-10).* This is because different probes in "the set" have different targeting arms. *Id.*

All MIPs in a "set" share a target of-interest of a certain length, for example 50 base pairs . *Id.,* pg. 36 (18-21). Each MIP captures at least the entire length of that target of-interest (i.e., 50 bp). *Id.,* pg. 35 (25-27). Importantly, some of the MIPs capture additional bases 5' and 3' of that target of-interest (i.e., flanking sequence). *Id.,* pg. 35 (25-27), pg. 36 (18-21), and Figure 2. The MIPs do this by having different targeting arm— that is what is meant by a staggered probe

layout. A staggered probe layout is shown in Figure 2 reproduced below.

Figure 2



Since the claimed staggered layout provides MIPs with increasing target lengths and different targeting arms, the claimed method will reliably capture the target even where a given one of the MIPs is incapable of hybridizing. *Id.,* pg. 34 (31) - pg. 35 (2).

The cited references fail to disclose a probe set comprising a plurality of MIPs having a staggered layout.

Akhras reports a one-primer multiplex DNA amplification system. *Akhras, Abstract.* Akhras reports Connector Inversion Probes (CIPers) containing 3' and 5' regions that bind to regions flanking a target, and then are circularized to enrich the target DNA. *Id.,* FIG. 1 and related description. Akhras reports a single CIPer for each of its targets. *Id.,* Table S1. Akhras reports that combining its CIPers with unique barcodes allows for the analysis of multiple parallel samples, thereby reducing the cost of microarray chips and sequencing reactions. *Id. pg. 4, col. 1.* Akhras provides no concern as to inefficient probe hybridization.

Akhras reports a single CIPer for each target nucleic acid sequence, and does not report or suggest a probe set, comprising a plurality of different MIPs, with a staggered layout such that

the MIPs of the probe set capture not only the target nucleic acid sequence, but also additional flanking sequence, as is required by the present claims. Since, Akhras provides no concern as to inefficient probe hybridization, and since Akhras is concerned with making a more efficient and cost effective assay, one of skill in the art would not have had reason or even motivation to contemplate using multiple probes that capture the same target nucleic acid as a sub-region of different targets of varying lengths in order to avoid problematic nucleic acids, as doing so would be in direct contrast with Akhras' one-probe per target cost-saving solution.

Chee fails to cure the deficiencies of Akhras.

Chee reports probes immobilized on a chip that are used for comparing a reference sequence with a target sequence to identify mutations in the target sequence. *Chee, Abstract.* Chee reports a probe tiling strategy that comprises a block of probes having identical 3' and 5' sequences with the variation confined to a central segment containing the interrogation positions (i.e., the variant positions). *Chee,* pg. 38 (23-27) and Figure 9.

Chee teaches away from the claimed staggered probe layout. Chee requires its probes to have identical 5' and 3' sequences. Those requirements are simply incompatible with the claimed requirement of variability in the MIP targeting arms required to hybridize upstream and downstream of targets of varying lengths. Since the claimed MIPs have varying target lengths, they simply cannot have the identical 3' and 5' targeting arms that are explicitly required by Chee.

Applicant submits that like Akhras and Chee, the combination of Bhangale, Hardenbol, and Akhras also fail to teach or suggest the presently claimed invention because they too fail to provide an element of the claims.

Bhangale reports an algorithm that identifies heterozygous individuals, which permits the discovery of low-frequency indels. *Bhangale, Abstract.* Bhangale simply reports an algorithm that helps to automate large-scale identification and genotyping of small indels from sequence trace data, something that was previously done on a small scale and manually. *Id.,* pg. 1457, col.

2. Bhangale does not report or suggest a probe set, comprising a plurality of different MIPs, with a staggered layout such that the MIPs of the probe set capture not only the target nucleic acid sequence, but also additional flanking sequence, as is required by the present claims. These claim elements are wholly missing from Bhangale. The secondary references of Hardenbol and Akhras fail to cure the deficiencies of Bhangale.

Hardenbol reports multiplexed genotyping with sequence-tagged MIPs as an efficient technology for large scale SNP analysis. *Hardenbol, Abstract.* Hardenbol reports the need to identify inexpensive per SNP methods to perform personalized whole-genome association studies. *Id.,* pg. 673, col. 1. Hardenbol presents a strategy that uses padlock probes with universal tag sequences that can identify more than 1,000 genotypes simultaneously. *Id.,col. 2.* Though Hardenbol reports the use of MIPs, Hardenbol reports that its strategy uses locus-specific probes to avoid the need for balancing allele-specific probes at every locus, and thus only one probe per locus is needed. *Id.,* pg. 674, col. 1 (emphasis added). Hardenbol reports that its one probe per locus provides an inexpensive method that allows the power of whole-genome analysis to be realized. *Id.,* pg. 677, col. 1.

Furthermore, Hardenbol states that cross-reactions are greatly suppressed because the second recognition sequence hybridizes instantaneously after the first and that DNA ligase ligates only perfectly hybridized DNA. *Id.,* pg. 676, col. 1-2. Therefore, Hardenbol is not concerned with inefficient probe hybridization because its probes are highly specific, and thus is not concerned with any type of redundant coverage. Instead, Hardenbol is only concerned with the breadth of coverage, using only one probe per locus to achieve whole genome sequencing. Thus, one of skill in the art would not have had reason or even motivation to contemplate using multiple probes for one target, as Hardenbol teaches away from such redundancy by requiring only one probe per target.

As discussed above, Akhras reports a single CIPer for each of its targets. *Akhras,* Table S1. Like Hardenbol and Benghale, Akhras fails to teach or suggest a MIP probe set having a

staggered layout. Even if combined with Benghale and Hardenbol, together they simply fail to teach or suggest a probe set having a staggered layout.

Accordingly, none of the cited references, alone or in combination, teach or suggest a probe set comprising a plurality of different MIPs having a staggered layout such that the MIPs of the probe set capture not only the target nucleic acid sequence, but also additional flanking sequence, as is required by the present claims. It is impermissible to sustain a rejection when not a single reference is presented that shows an element of the claims. How can a missing element be obvious when it is not even disclosed in the prior art?

Applicant submits that the arguments presented above make it clear that the claims of the Applicant's invention are not obvious in view of the cited references. Accordingly, Applicant submits that all of the 35 U.S.C. §103 rejections are overcome.

Double Patenting Rejections

The Office Action, at page 14, states that claims 1, 4 and 68 are rejected on the ground of non-statutory double patenting over claims 1-15 of U.S. Patent No. 9,115,387; at page 17, claims 1, 3-4, and 68 over claims 1-15 of U.S. Patent No. 8,778,609; at page 20, claims 1, 3-4, and 68 over claims 1-15 of U.S. Patent No. 9,677,124; and at page 23, claims 1, 3-4, and 68 over claims 16-30 of U.S. Patent No. 10,202,637.

Applicant submits the amendments to the claims differentiate the pending claims from the claims of U.S. Patent No. 9,115,387; U.S. Patent No. 8,778,609; U.S. Patent No. 9,677,124; and U.S. Patent No. 10,202,637. The pending claims are directed to a MIP probe set having a staggered layout and the claims of U.S. Patent No. 9,115,387; U.S. Patent No. 8,778,609; U.S. Patent No. 9,677,124; and U.S. Patent No. 10,202,637 are directed to tiling MIPs.

Applicant submits that staggering comprises probes that capture the entire target nucleic acid, plus additional sequences, where tiling comprises probes that only capture portions or sub-regions of the entire target nucleic acid. *As-filed application, e.g.,* Figures 1 and 2. Accordingly,

staggering MIPs and tiling MIPs are substantially different strategies, therefore the claims drawn to the different strategies cannot be the same.

Applicant believes that the claim amendments address and overcome all grounds of non-statutory double patenting.

Petitioner Illumina, Inc., EX1002, p. 1782

Conclusion

Applicant respectfully submits that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: April 21, 2020

Respectfully submitted,
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Petitioner Illumina, Inc., EX1002, p. 1783

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8	6082

21710 7590 06/09/2020

BROWN RUDNICK LLP
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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
06/09/2020	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.** 13/266,862	**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 4/21/2020.

☐ 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) 1,3-4 and 68-69 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) 1,3-4 and 68-69 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: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. 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 4/21/2020.

Claims 1, 3-4,68-69 are pending.

Claims 2, 5-67 have been canceled.

Claim 69 has been added by amendment.

Claims 1 , 4, 68 are identified as amended. However, claim 4 does not have any marks for amendment as required by 37 CFR 1.121. Thus the response is non-compliant with 37 CFR 1.121. However in order to promote compact prosecution and customer service the response will be examined, however future amendments that are not compliant with 37 CFR 1.121 may not be entered or examined.

Claims 1, 3-4 and 68-69 are being examined.

Any rejection or objection not reproduced below has been withdrawn upon further consideration.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 2/5/2020 is being considered by the examiner.

Claim Rejections - 35 USC § 103

3. 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.

4. Claim 1, 4, 68-69 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Akhras et al (PLOS one (2007) volume 2 (9) e915 and supplemental table) (IDS 3/28/2013) and Chee et al (WO 95/11995).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable

interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the nucleic acid wherein the probe set has a staggered layout such that all of the MIPs capture at least the target, and some MIPs in the probe set capture additional flanking sequence;." The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

The specification provides no definition of staggering. The specification states on page 35 that a set of probes:

"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 MTPs used to capture aven molecule".. Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign=sd&utm_medium=serp&utm_source=jsonld, downloaded 6/3/2020) defines Stagger: stagger adjective Definition of stagger (Entry 3 of 3): marked by an alternating or overlapping pattern." In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be the positioning of probes of a set or plurality of probes that allow for inclusion of additional flanking nucleotides for hybridization.

Akhras teaches, "The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay [17], which includes: i) probe hybridization, single "G" base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by relinearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target (Figure 1B). The 39end of the probe, which we call the Extension Site (ES), primes for polymerization, while the 59end serves as point of ligation and is referred to as the Anchor Site (AS) (Figure 1). With all four dNTPs present, the polymerase is capable of extending past the intended point of ligation, generating a false negative. To address this problem, probes were designed to have an annealing temperature of approximately 5 degrees higher for the AS than

that of the ES. The AS therefore blocks DNA extension when using a polymerase deficient in strand displacement at an appropriate intermediate temperature (50uC). For enhanced sensitivity and specificity a vast variety of probe concentrations and thermoprofiles were explored. Probes used in the 10–100 fmol concentration range yielded the strongest signal. Higher cycle numbers and shorter annealing times created a more efficient thermoprofile. The CIPer method successfully genotyped 1 pg of plasmid DNA in the presence of 200 ng non-reacting human genomic DNA, without generating any false positives (Figure S1). Assay optimizations were based on genotyping of HPV plasmid 56, validated by either SYBR GREEN assay or agarose gel electrophoresis, followed by Pyrosequencing verification (see Results, The Conserved Sequence Primer Connector Inversion Probe (CSP-CIPer)).”

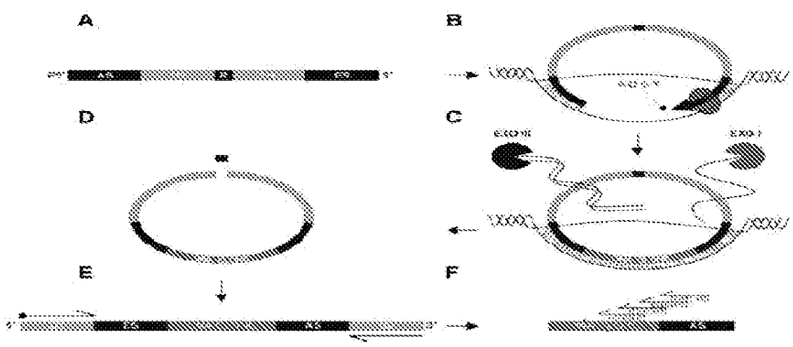


Figure 1. Schematic overview of Connector Inversion Probe (CIPer) technology. A) Synthetic oligonucleotide containing regions i) *AS and ES* (anchor site and extension sites): approximately 20 base pair fragments homologous to regions flanking target of interest, ii) *R*: restriction site for probe linearization, iii) *U1 and U2*: universal primer regions for inverted probe amplification. B) Target rescue through complete gap filling by a DNA polymerase and ligation-based probe circularization. C) Circular DNA enrichment through degradation of linear DNA by enzymes Exonuclease I and III, which are deactivated prior to the next step. D) Probe linearization by restriction site cleavage. E) Inverted probes are amplified with universal primers; one is biotinylated for subsequent amplicon validation. F) Amplicon validation using multiple sequencing primers.
doi:10.1371/journal.pone.0009515.g001

With regards to claims 1, 4, 68, Akhras teaches, “CIPer detection was also applied to screening of resistance mutations in Neisseria gonorrhoeae. Two CIPers were used to perform a duplex amplification in a single-tube of the genes gyrA and parC [23], which are known to mutate easily and by specific SNPs generate resistance to

ciprofloxacin and other quinolone antibiotics. The CIPers were designed with CIP creator 1.0.1 (http://bioel.stanford.edu/CIPer) based on previously described PCR primer-pairs not originally intended for multiplex PCR [21]. We intentionally inverted the gyrA CIPer to target the negative strand, while the parC CIPer targeted the positive strand, to illustrate that CIPers can be used on both DNA strands. In the case of close target proximities, it might be wise to revise such a strategy. Mutations on amino acid residues S91 and D95 for gyrA, and E91 for parC were the particular subjects of our interrogation. There are many other candidate genes for future CIPer-based epidemiological studies of antibiotic resistance [31]."

Thus Akhras teaches providing a sample comprising a target nucleic acid (DNA clone), contacting the sample with a plurality of probes that flank two different resistance mutations in two different Neisseria gonorrhoeae genes of the Neisseria gonorrhoeae chromosome that do not overlap in the 5' region and the 3' region, converting the hybridized probe to a plurality of circularized probes comprising the target sequences, isolating the probes and sequence the target nucleic acids.

Arkhas does not specifically teach MIP probe sets which allow for additional flanking nucleotides to be hybridized.

However, Chee et al teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant

sites and immediately adjacent bases" (page 18). Chee teaches, " The first probe set often has at least 100 interrogation positions corresponding to 100 contiguous nucleotides in the reference sequence. Sometimes the first probe set has an interrogation position corresponding to every nucleotide in the reference sequence.an array of capture probes" (page 3, 1st full paragraph)) Chee exemplifies by using a block tiling arrays to determine nucleic acid sequences of chosen sites and adjacent bases (see Figure7 and page 37 line 10- page 38 line 34). Each tiling probe comprises

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use MIPS with suitable arrays such as block tiling arrays. The artisan would be motivated to detect mutations near known SNPs or nucleotides of interest, as exemplified by Chee. In addition, one of ordinary skill in the art would have been motivated to employ overlapping and/or staggered probe sets/arrays in addition to or as a substitution of titling arrays in the meth9od of Arkhas. One of ordinary skill in the art would have motivated to employed obvious patterning variants as a matter of design choice in order to enhance suitable captures of flanking residues of target hybridization sites, as suggested by Chee. The artisan would have a reasonable expectation of success as the artisan is merely using known methods or strategies of designing MIPS to analyze known sequences.

With regards to claim 69, Arkhas teaches 100bp target (figure 2).

Response to Arguments

The response traverses the rejection by reproducing figure 2, which provides a schematic of what a staggered probe layout could be, but does not define a staggered probe.

The court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from 'reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.). See also In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997).

Further Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign=sd&utm_medium=serp&utm_source=jsonld, downloaded 6/3/2020) defines Stagger: stagger adjective Definition of stagger (Entry 3 of 3): marked by an alternating or overlapping pattern. Thus the definition of staggered definition is not consistent with the narrow interpretation of the claims provided by the response.

Thus as the specification provides a preferred embodiment of staggered layout, but does not define staggered layout and the plain meaning of stagger is broader than the interpretation of the response wishes, this argument is not persuasive. It is noted if applicant's wish for the interpretation consistent with the embodiment, applicant can amended the claims to recite all the limitations of embodiment. It is noted this would provide new limitations and require further search and consideration after final rejection.

The response continues by reviewing the representative's opinion of the teachings of Arkhas and asserting that Arkhas does not teach all the limitations of the claims. This argument has been thoroughly reviewed but is not considered persuasive as the instant rejection is an obviousness type rejection.

The response continues by arguing the Arkhas does not discuss the inefficient probe hybridization. This argument has been thoroughly reviewed but is not considered persuasive as the claims provide no limitation with respect to probe hybridization.

The response continues by asserting the teachings of Chee does not correct deficiencies. The response continues by asserting Chee every probe has the same flanking sequences and thus teaches away. This argument has been thoroughly reviewed but is not considered persuasive as Chee teaches, "The first probe set often has at least 100 interrogation positions corresponding to 100 contiguous nucleotides in the reference sequence. Sometimes the first probe set has an interrogation position corresponding to every nucleotide in the reference sequence." Thus this argument is not persuasive.

5. Claim 1, 3-4, 68 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Macevicz (US PGPUB 2005/0250147) and Abravaya et al, Nucleic Acids Research, 23: 675-682 (1995); .

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the nucleic acid wherein the probe set has a staggered layout such that all of the MIPs capture at least the target, and some MIPs in the probe set capture additional flanking sequence;." The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

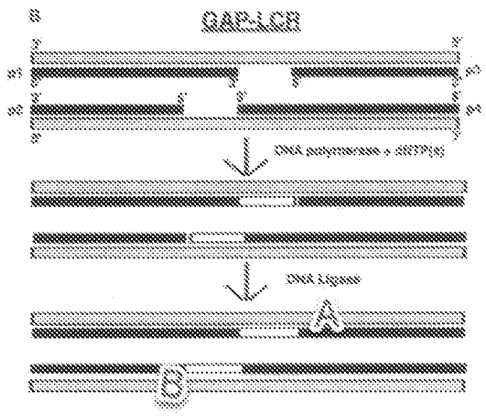
The specification provides no definition of staggering. The specification states on page 35 that a set of probes:

"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 MTPs used to capture aven molecule".. Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign=sd&utm_medium=serp&utm_source=jsonld, downloaded 6/3/2020) defines Stagger: stagger adjective Definition of stagger (Entry 3 of 3): marked by an alternating or overlapping pattern." In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be the positioning of probes of a set or plurality of probes that allow for inclusion of additional flanking nucleotides for hybridization.

Macevicz teaches methods of hybridization using tags to detect nucleic acids (abstract). Macevicz teaches the use of selectable probes including MIPS and padlock probes.(0052, 0062).Macevicz teaches these probes allow for template driven circularization dependent on the presence of the template nucleic acid. Macevicz teaches the probes can be gap ligation probes of Abravaya (0054). Maceviz teaches digestion of non-circularized probes (0062) or isolation by use of a capture moiety (0052).

Abravaya teaches GAP-LCR (title, figure 1.) Abravaya teaches



Thus DNA polymerase fill in of A captures additional flanking sequences than the DNA polymerase fill in of B.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use probes taught by Abravaya in the method of Macevicz. The artisan would be motivated to as Macevicz specifically suggests the use of such probes in 0054. The artisan would have a reasonable expectation of success as the artisan is using known probes in known methods.

With regards to claim 3-4, the sequence of the target arms immediately adjacent to the region filled in by DNA polymerase in A are non-overlapping (different) with targets arms immediately adjacent to the region filled in by DNA polymerase in B.

With regards to claim 68, Macevicz teaches a gap of several nucleotides (0063).

Response to Arguments

This is a new grounds of rejection in view of the amendment.

6. Claim 69 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Macevicz (US PGPUB 2005/0250147) and Abravaya et al, Nucleic Acids Research, 23: 675-682 (1995) as applied to claim 1, 3-4, 68 above, and further in view of Akhras et al (PLOS one (2007) volume 2 (9) e915 and supplemental table) (IDS 3/28/2013).

The teachings of Macevicz and Abravaya are set forth above.

While, Macevicz teaches a gap of several nucleotides (0063).

Macevicz and Abravaya do not specifically teach a target nucleic acid of at least 50 nucleotides flanked by 5' and 3' targeting arms.

However, Arkhas teaches 100bp target (figure 2) flanked by target sequencings.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to provide a gap of 100 nucleotides in the method of Macevicz and Abravaya. The artisan would be motivated to increase the size of sequence being assayed. The artisan would have a reasonable expectation of success as Arkhas teaches larger sequences work.

Response to Arguments

This is a new grounds of rejection in view of the amendment.

Double Patenting

7. 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.

8. Claims 1, 4 , 68 rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 9,115,387.

The instant claims are 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 nucleic acid, wherein the probe set has a staggered layout such that all of the MIPs capture at least 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; isolating the plurality of circularized probes; and analyzing the target.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the nucleic acid wherein the probe set has a staggered layout such that all of the MIPs capture at least the target, and some MIPs in the probe set capture additional flanking sequence;." The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

The specification provides no definition of staggering. The specification states on page 35 that a set of probes:

"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 MTPs used to capture aven molecule".. Merriam-Webster.com (https://www.merriam-

websier.com/dictionary/staggered?utm_campaign=sd&utm_medium=serp&utm_source=jsonld, downloaded 6/3/2020) defines Stagger: stagger adjective Definition of stagger (Entry 3 of 3): marked by an alternating or overlapping pattern." In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be the positioning of probes of a set or plurality of probes that allow for inclusion of additional flanking nucleotides for hybridization.

Claim 1 of 387 requires, "A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; fragmenting the nucleic acid template to produce a plurality of fragments; tiling a plurality of molecular inversion probes across a portion of at least one of the fragments, wherein immediately adjacent probes hybridize to opposite strands of the at least one fragment and probes on the same strand hybridize to the at least one fragment in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the at least one fragment, thereby obtaining sequence information about the nucleic acid template"

Claim 2 of 387requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting amendment has overcome the rejection. The response continues by asserting claims which capture the entire target sequence plus additional sequence is not obvious over the tiling arrays of the rejected patents. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not define what is required of "a target" and recitation of "a" prior to target allows for interpretation of multiple target sequences.

9. Claims 1, 3-4 and 68 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 8,778,609. This is a nonstatutory double patenting rejection.

The instant claims are 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 nucleic acid, wherein

the probe set has a staggered layout such that all of the MIPs capture at least 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; isolating the plurality of circularized probes; and analyzing the target.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the nucleic acid wherein the probe set has a staggered layout such that all of the MIPs capture at least the target, and some MIPs in the probe set capture additional flanking sequence;." The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

The specification provides no definition of staggering. The specification states on page 35 that a set of probes:

"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 MTPs used to capture aven molecule".. Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign=sd&utm_medium=serp&utm_source=jsonld, downloaded 6/3/2020) defines Stagger: stagger adjective Definition of stagger (Entry 3 of 3): marked by an alternating or overlapping pattern." In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be the positioning of probes of a

set or plurality of probes that allow for inclusion of additional flanking nucleotides for hybridization.

Claim 1 of 609 requires, "1. A method for analyzing a nucleic acid template, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template."

Claim 2 of 609 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting amendment has overcome the rejection. The response continues by asserting claims which capture the entire target sequence plus additional sequence is not obvious over the tiling arrays of the rejected patents. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not define what is required of "a target" and recitation of "a" prior to target allows for interpretation of multiple target sequences.

10. Claims 1, 3-4 and 68 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 9,677,124. This is a nonstatutory double patenting rejection.

The instant claims are 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 nucleic acid, wherein the probe set has a staggered layout such that all of the MIPs capture at least 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; isolating the plurality of circularized probes; and analyzing the target.

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be

understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the nucleic acid wherein the probe set has a staggered layout such that all of the MIPs capture at least the target, and some MIPs in the probe set capture additional flanking sequence;." The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

The specification provides no definition of staggering. The specification states on page 35 that a set of probes:

"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 MTPs used to capture aven molecule".. Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign=sd&utm_medium=serp&utm_source=jsonld, downloaded 6/3/2020) defines Stagger: stagger adjective Definition of stagger (Entry 3 of 3): marked by an alternating or overlapping pattern." In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be the positioning of probes of a set or plurality of probes that allow for inclusion of additional flanking nucleotides for hybridization.

Claim 1 of 124 requires, "a method for identifying an allelic status of a subject, the method comprising: obtaining a sample comprising a nucleic acid template from a subject; tiling a plurality of molecular inversion probes across both alleles of a locus on the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an

overlapping manner; filling in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; analyzing the filled-in region of a plurality of the probes to obtain sequence information about both alleles of the locus; and identifying an allelic status based on the sequence information.."

Claim 2 of 124 requires, "2. The method according to claim 1, wherein analyzing is by sequencing."

Dependent claim 7 requires, "The method according to claim 6, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting amendment has overcome the rejection. The response continues by asserting claims which capture the entire target sequence plus additional sequence is not obvious over the tiling arrays of the rejected patents. This argument has been thoroughly reviewed but is not considered persuasive

as the claims do not define what is required of "a target" and recitation of "a" prior to target allows for interpretation of multiple target sequences.

11. Claims 1, 3-4 and 68 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 16-30 of U.S. Patent 10202637 No from allowed application 15/620129. This is a nonstatutory double patenting rejection.

The instant claims are 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 nucleic acid, wherein the probe set has a staggered layout such that all of the MIPs capture at least 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; isolating the plurality of circularized probes; and analyzing the target.

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "wherein the targeting arms of each MIP hybridize upstream and downstream of a target in the nucleic acid wherein the probe set has a staggered layout such that all of the MIPs capture at least the target, and some MIPs in the probe set capture additional flanking sequence;." The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target nucleic acid is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

The specification provides no definition of staggering. The specification states on page 35 that a set of probes:

"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 MTPs used to capture aven molecule".. Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign=sd&utm_medium=serp&utm_source=jsonld, downloaded 6/3/2020) defines Stagger: stagger adjective Definition of stagger (Entry 3 of 3): marked by an alternating or overlapping pattern." In view of the guidance and art of record the amendment provides the probe set are "staggered" by the broadest reasonable interpretation. This appears to be the positioning of probes of a set or plurality of probes that allow for inclusion of additional flanking nucleotides for hybridization.

The independent claim 16 of 129 requires, "A method for reducing and/or detecting bias associated with capture, amplification and sequencing of nucleic acid, the method comprising: obtaining a sample comprising a nucleic acid template; tiling a plurality of molecular inversion probes across a portion of the template, wherein immediately adjacent probes hybridize to opposite strands of the nucleic acid template and probes on the same strand hybridize to the template in an overlapping manner, and wherein each molecular inversion probe comprises a unique differentiator tag sequence; filling-in a region between targeting arms of a plurality of the molecular inversion probes with nucleotides; and analyzing the filled-in region of a plurality of the probes to obtain sequence information about the nucleic acid template, wherein the

sequence information comprises the differentiator tag sequences; identifying bias based on the sequence information.."

Dependent claim 17 requires, "The method according to claim 16, wherein analyzing is by sequencing."

Dependent claim 22 requires, "The method according to claim 21, wherein the mutation is selected from the group consisting of: a single nucleotide polymorphism (SNP), an insertion, a deletion, an inversion, a translocation, a substitution, and a combination thereof."

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made the detection of an insertion in one copy of a genome would result in an additional flanking sequence of the 5' and 3' region of the probe that do not overlap with other 5' and 3' regions of the probe. The artisan would be motivated as a nucleic acid without an insertion would have a different sequence then a nucleic acid with an insertion. The artisan would have a reasonable expectation of success as the artisan is merely performing the method of a US patent.

Response to Arguments

The response traverses the rejection asserting amendment has overcome the rejection. The response continues by asserting claims which capture the entire target sequence plus additional sequence is not obvious over the tiling arrays of the rejected patents. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not define what is required of "a target" and recitation of "a" prior to target allows for interpretation of multiple target sequences.

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Summary

No claims are allowed.

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.

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 https://ppair-my.uspto.gov/pair/PrivatePair. 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. 13/266,862	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-20050250147-A1	11-2005	Macevicz, Stephen C.	C12Q1/6809	435/6.12
	B					
	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	Merriam-Webster.com (https://www.merriam-webster.com/dictionary/staggered?utm_campaign=sd&utm_medium=serp&utm_source=jsonld, downloaded 6/3/2020)
	V	Abravaya et al, Nucleic Acids Research, 23: 675-682 (1995);
	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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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)	2020-02-05
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)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13266862
Filing Date	2012-03-13
First Named Inventor	Gregory Porreca
Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	MLB-002/01US 34468/8

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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
/SP/	1	8114027		2012-02-14	Triva	

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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
/SP/	1	20140228226	A1	2014-08-14	Yin et al.	
/SP/	2	20110288780	A1	2011-11-24	Rabinowitz et al.	
/SP/	3	20120270739	A1	2012-10-25	RAVA et al.	
/SP/	4	20150051085	A1	2015-02-19	Vogelstein et al.	
/SP/	5	20170044610	A1	2017-02-16	Johnson	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

/SP/	6	20140342354	A1	2014-11-20	Evans et al.	
/SP/	7	20040121373	A1	2004-06-24	Friedlander et al.	
/SP/	8	20040053275	A1	2004-03-18	Shafer	

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/SP/	1	2011066476	WO	A1	2011-06-03	Quantalife, Inc		
/SP/	2	2011067378	WO	A1	2011-06-09	Olink Genomics Ab		
/SP/	3	2007/061284	WO	A1	2007-05-31	Plant Res Int BV		

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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]
/SP/	1	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	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

/SP/	2	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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EXAMINER SIGNATURE

Examiner Signature	/Steven Pohnert/ (06/03/2020)	Date Considered	06/03/2020

*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:	40792426
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	08-OCT-2020
Filing Date:	13-MAR-2012
Time Stamp:	15:48:15
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1110
RAM confirmation Number	E202008F48285190
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	Request for Continued Examination (RCE)	34468_8US_-_Request_for_Continued_Examination_Fillable_PDF.pdf	1379006 c7f79ecf9c21637c862ff76c50be8a337d92f0a7	no	3
Warnings:					
Information:					
2		MLB-002-01US-FOA-Response.pdf	54962 d087831c3758b1783e8e89af2e4dbd0213ece9e4	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment Submitted/Entered with Filing of CPA/RCE	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	7

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32410 54ae5538e8b1d957e94cb6b25b60cc8d78d9f09c	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1466378	

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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.

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	13266862	Filing Date	2012-03-13	Docket Number (if applicable)	MLB-002/01US 34468/8	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
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Signature of Registered U.S. Patent Practitioner			
Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2020-10-08
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.

Attorney Docket No. MLB-002/01US 34468/8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
APPL. NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

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

FILED ELECTRONICALLY

RESPONSE

This paper is in response to the final Office Action mailed June 9, 2020, from the United States Patent and Trademark Office. A Request for Continued Examination is submitted herewith. Applicant petitions for and requests a one-month extension of time.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

Applicant submits the EOT and RCE fees herewith and authorizes the Commissioner to charge any additional required fees to Deposit Account No. 50-0369.

Amendments to the Claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently Amended) A method for analyzing a target nucleic acid, the method comprising:

providing a sample comprising nucleic acid comprising a target region;

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 on either side ~~upstream and downstream~~ of ~~a~~ the target region in the nucleic acid, wherein ~~the probe set has a staggered layout such that all of~~ the MIPs capture at least the target region, and, wherein some MIPs in the probe set capture additional flanking sequence of various lengths;

converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target and some comprising additional flanking sequences of various lengths;

isolating the plurality of circularized probes; and

analyzing the target region.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

4. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, different than the sequences of the 5'

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targeting arm and the 3' targeting arm of each other probe.

5-67. (Canceled)

68. (Currently Amended) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized on either side of ~~to~~ the target region, are separated by a plurality of nucleotides on the nucleic acid~~target~~.

69. (Currently Amended) The method of claim 1, wherein the target region comprises at least 50 base pairs of DNA.

Remarks

Claims 1, 3, 4, and 68-69 are pending in the application, with claim 1 being the only independent claim. Claims 1, 68, and 69 are amended. Support for the claim amendment and the new claim can be found throughout the as-filed application, for example at pages 35-36 and Figure 2. No new matter is added.

Rejections under 35 U.S.C. §103

Claims 1, 4, 68, and 69 are rejected under 35 U.S.C. §103 over Akhras, et al., (PLOS one, 2007, 2(9):e915 and supplemental table) and Chee, et al. (WO 95/11995). Claims 1, 3, 4, and 68 are rejected under 35 U.S.C. §103 over Macevicz (US 2005/0250147) and Abravaya, et al. (Nucleic Acids Research, 23: 675-682 (1995)). Claim 69 is rejected under 35 U.S.C. §103 over Macevicz, Abravaya, and Akhras.

Applicants note that the Patent Office has the initial burden of making a prima facie case for obviousness. ACCO Brands Corp. v. Fellowes, Inc., 813 F.3d 1361, 1365–66, 117 USPQ2d 1951, 1553-54 (Fed. Cir. 2016). Here, the Patent Office cannot make its prima facie case because elements of the claims are not reported in the cited art. Without the missing elements, Applicants submit that it is impossible to make a prima facie case that the cited references show the elements of the invention. Moreover, no suggestion to alter the prior art to add the missing element has been made.

Independent claim 1 is a method of nucleic acid analysis in which each of a plurality of molecular inversion probes (MIPs) has two targeting arms that hybridize on either side of a target region in the nucleic acid. As a result, each MIP captures the same target region. The claims further require that some of the MIPs capture additional flanking sequence.

Applicant submits that none of the cited references disclose sets of MIPs in which each MIP captures the same target region and in which some of the MIPS additionally capture flanking sequence. In light of the fact that these elements are missing in the cited art, Applicant

Petitioner Illumina, Inc., EX1002, p. 1832

believes that the Office has not made its prima facie case for obviousness.

The Office Action maintains that the specification provides no definition of staggering and that the arguments presented in the previous response regarding a staggered probe layout are narrower than the broadest reasonable interpretation. Applicant respectfully submits that the amended claims clarify the claims.

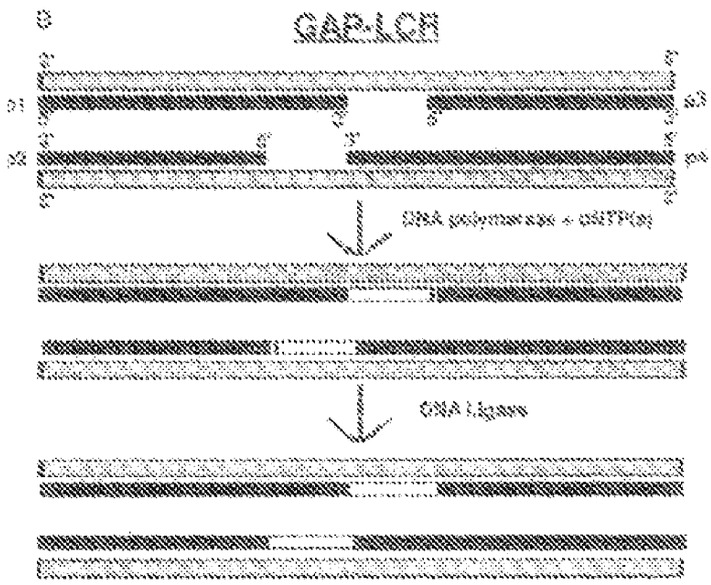
With respect to the cited art, Akhras reports a one-primer multiplex DNA amplification system. *Akhras, Abstract.* Akhras reports Connector Inversion Probes (CIPers) containing 3' and 5' regions that bind to regions flanking a target, and then are circularized to enrich the target DNA. *Id.,* FIG. 1 and related description. Akhras only shows a one-primer system with a single anchor site and extension site that are homologous to regions flanking a target of interest. Accordingly, Akhras reports the capture of an identical sequence that includes the target. In contrast, the present claims specify that, while all of the MIPs capture the target region, some capture additional flanking sequences of various lengths. That will not happen in the methods reported by Akhras.

Chee fails to cure the deficiencies of Akhras.

Chee reports probes immobilized on a chip that are used for comparing a reference sequence with a target sequence to identify mutations in the target sequence. *Chee, Abstract.* Chee reports a probe tiling strategy that includes a block of probes having identical 3' and 5' sequences with the variation confined to a central segment containing the interrogation positions (i.e., the variant positions). *Chee,* pg. 38 (23-27) and Figure 9. Accordingly, Chee, like Akhras fails to teach or suggest a probe set of MIPs that all capture the same target region with some of the MIPs also capturing various lengths of flanking sequences.

Like Akhras and Chee, Macevicz and Abravaya are missing the same element of the present claims. Macevicz reports hybridization-based assays using probes specific for the same target polynucleotide. Macevicz, Abstract. Macevicz does not disclose a probe set of MIPs with each MIP in the set capturing the same target region of nucleic acid and some of the MIPs

capturing additional flanking sequences of various lengths. Abravaya reports a modified (GAP) ligase chain reaction (LCR) that uses two pairs of synthetic oligonucleotides to hybridize to adjacent positions of complementary strands of a target DNA. The Office Action points to FIG. 1B of Abravaya, reproduced below:



The Office Action argues that the DNA polymerase fill in of the two probe sets capture different flanking sequences and, therefore, teaches the present claims. Applicant respectfully disagrees with this characterization of Abravaya. As described in the caption to FIG. 1, the two probes sets are hybridized to complementary strands of target DNA and, therefore, are not capturing the same target region of nucleic acid but, instead, complementary sequences. Furthermore, as described in the caption, Abravaya teaches that target sequence is represented by the entire shaded bars (and not a single nucleotide) and, therefore, no additional flanking sequence can be captured in the methods of Abravaya.

Because the claim element of a probe set of MIPs that all capture the same target region with some of the MIPs also capturing various lengths of flanking sequences is wholly missing from all of the cited references, Applicant believes that the rejections under section 103 are

overcome.

Double Patenting Rejections

Claims 1, 4, and 68 are rejected on the ground of non-statutory double patenting over claims 1-15 of U.S. Patent No. 9,115,387. Claims 1, 3-4, and 68 are rejected on the ground of non-statutory double patenting over claims 1-15 of U.S. Patent No. 8,778,609, claims 1-15 of U.S. Patent No. 9,677,124, and claims 16-30 of U.S. Patent No. 10,202,637.

As discussed above, the Applicant submits that the amended claims incorporate specific elements of the staggered layout described in the specification and forwarded in the arguments of the prior response. Applicant submits that those amendments differentiate the pending claims from the claims of U.S. Patent No. 9,115,387; U.S. Patent No. 8,778,609; U.S. Patent No. 9,677,124; and U.S. Patent No. 10,202,637. The amended claims are directed to a MIP probe set having a staggered layout as detailed above while the claims of U.S. Patent No. 9,115,387; U.S. Patent No. 8,778,609; U.S. Patent No. 9,677,124; and U.S. Patent No. 10,202,637 are directed to tiling MIPs. Accordingly, Applicant believes that the double patenting rejections are overcome.

Conclusion

Applicant respectfully submits that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: October 8, 2020

Respectfully submitted,
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Attorney for Applicant
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Petitioner Illumina, Inc., EX1002, p. 1835

Electronic Patent Application Fee Transmittal

Application Number:	13266862
Filing Date:	13-Mar-2012
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-002/01US 34468/8

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

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 $0 paid	2251	1	110	110
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	1000	1000
		Total in USD ($)		**1110**

Electronic Acknowledgement Receipt

EFS ID:	41643241
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	14-JAN-2021
Filing Date:	13-MAR-2012
Time Stamp:	16:50:54
Application Type:	U.S. National Stage under 35 USC 371

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	Information Disclosure Statement (IDS) Form (SB08)	34468_8US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1037641 ed056349f06a8d5a4a8a749b72947491fe06f92f	no	11

Warnings:

Information:					
2	Foreign Reference	EP2716766A1.pdf	2282683 1f8a94f2c8908b74ad768220bdb4777d1bc6bb5a	no	40
Warnings:					
Information:					
3	Foreign Reference	WO1996019586.pdf	1044274 a16821bf77614a932b76010347f497430cef03fa	no	27
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	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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Name/Print	Thomas C. Meyers	Registration Number	36,989

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	18	Treangen, 2011, Repetitive DNA and next-generation sequencing: computational challenges and solutions, Nat Rev Gen 13(1):36-46	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

	19	Turner, 2009, Massively parallel exon capture and library-free resequencing across 16 genomes, Nat Meth 6:315-316	
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	21	Zhulidov, 2004, Simple cDNA normalization using kamchatka crab duplex-specific nuclease, Nucl Acids Res 32(3):e37	
	22	Zimran, 1990, A glucocerebrosidase fusion gene in Gaucher disease, J Clin Invest 85:219-222	

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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8	6082

21710 7590 04/27/2021

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
04/27/2021	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

Office Action Summary	**Application No.** 13/266,862	**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 10/8/2020.

☐ 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) 1,3-4 and 68-69 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) 1,3-4 and 68-69 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 4/8/2013 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.

Continued Examination Under 37 CFR 1.114

2. 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 10/8/2020 has been entered.

Claim Status and Formal matters

This action is in response to papers filed 10/8/2020.

Claims 1, 3-4,68-69 are pending.

Claims 2, 5-67 have been canceled.

Claim 69 has been added by amendment.

Claims 1, 68-69 are identified as amended.

Claims 1, 3-4 and 68-69 are being examined.

Any rejection or objection not reproduced below has been withdrawn upon further consideration.

The previous art rejections have been withdrawn in view of the amendment to require flanking sequences with various lengths.

The ODP rejections have been withdrawn in view of the amendment to require flanking sequences with various lengths.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 1/14/2021 is being considered by the examiner.

Claim Rejections - 35 USC § 112

4. 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.

5. Claims 1, 3-4 and 68-69 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 applications subject to pre-AIA 35 U.S.C. 112, the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended to recite, "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 on either side -the target region in the nucleic acid, wherein the MIPs capture at least the target region, and, wherein some MIPs in the probe set capture additional flanking sequence of various lengths." The claim is functionally claiming how the MIPs relate to the flanking sequences, but provide no specific limitations or structure for the probes. The response asserts support can be found on page 35-36 and figure 2. The teachings state, "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 base pair is averaged across three probes. Targeting arms land immediately adjacent to the black or gray regions shown." Thus the teachings of the cited portions relate to 3 probes to a target and sub target. The only recitation of the specification of various with respect to various lengths, recites, "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

between50 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')." Thus the teachings with respect to various lengths are limited to probes that provide different lengths of flanking sequences due to variability with respect to the target sequences.

Thus the amendment to the claims lacks adequate written description.

Response to Arguments

This is a new ground of rejection.

Claim Rejections - 35 USC § 112

6. 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.

7. Claims 1, 3-4 and 68-69 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 applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claim 1 recites, "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 on either side the target region in the

nucleic acid, wherein the MIPs capture at least the target region, and, wherein some MIPs in the probe set capture additional flanking sequence of various lengths." The only recitation of various is with respect to example 5 which indicates the various lengths is dependent on the target sequence, not the targeting arms. Thus it is unclear how the wherein clause provides structure for the MIP.

Response to Arguments

This is a new ground of rejection.

Claim Rejections - 35 USC § 103

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 1, 38 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Daly (Clinical Chemistry (2007)volume 53, pages 1222-1230) and Hardenbohl (Genome Research (2005) volume 15, pages 269-275).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side the target region in the nucleic acid, wherein the MIPs capture at least the target region, and, wherein some MIPs in the probe set capture additional flanking sequence of various lengths." The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Daly teaches, " Molecular inversion probe (MIP) technology is an oligonucleotide-based method that can be used to analyze several thousand SNPs in a single assay (20). This technique has been used extensively for the HapMap project (21) and offers several advantages for multiplex genotyping. First, PCR amplification occurs after mutation detection, at which time MIPs have been converted to standard-length oligonucleotides of similar sequence composition utilizing common PCR primers. Second, the MIPs are designed to be locus-specific rather than allele specific and require only a single probe per marker, so any loss of performance of a probe will affect both alleles equally, avoiding unbalanced genotyping. Third, each probe has two recognition sequences as in PCR but retains unimolecular hybridization kinetics, enabling high multiplexing with low concentration requirements. Finally, the use of molecular tag sequences on the probes allows hybridization to the microarray to be independent of the gene sequence, increasing the specificity and sensitivity of detection and allowing for a high degree of flexibility in assay design (22)." (page 1223, 1st column top).

Daly continues, " We have applied MIP technology to develop an assay testing 1227 variants in 169 genes involved in drug metabolism. Within this set, we have chosen a core set of 165 variants in 27 genes for extensive analytical validation." (page 1223, 1st column, 2nd full paragraph).

Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

Daly does not teach the sequence of the probes or specifically teach probes with various flanking region.

However, it would have been prima facie oblivious to one of ordinary skill in the art at the time the invention was made a MIP to detect a SNP (target region) that detected an insertion would provide additional flanking sequences. The artisan would be motivated as Daly specifically teaches detection of SNPs and insertions and deletions. The artisan would have a reasonable expectation of success as the artisan is merely designing known probes.

Daly does not specifically converting to a closed circularized probe , isolating and analyzing.

However, Daly in the first cited paragraph references Hardenbohl (reference 20).

Hardenbohl teaches., "single oligonucleotide probe with recognition sequences at each terminus is hybridized with a genomic target sequence such that it forms a circular structure, with the ends of the probe abutting. This leaves a single base gap at the location of a SNP. This gapped-duplex is then tested in four separate reactions, each with a single dNTP species present, in which successful polymerization/ligation provides allelic differentiation. The probes are subsequently released from the genomic DNA and those that have been covalently circularized in the correct allele/nucleotide reaction combinations are amplified using a "universal" PCR primer pair. Each amplified probe contains a unique tag sequence that is complementary to a sequence on the universal tag array. Tags have been selected to have a similar Tm and base composition and to be maximally orthogonal in sequence complementarity. Amplicons are fluorescently labeled and the tag sequences released from the genome homology regions using a restriction endonuclease treatment. The tags are then detected using a complementary tag array." (MIP technology, page 270).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to circularize, isolate and analyze the MIP and target region. The artisan would be motivated as Daly specifically references Hardenbohl. The artisan would have a reasonable expectation of success as the artisan is using art accepted probes in an art accepted manner.

With regards to claim 68, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that the detection of an insertion by a probe designed to detect a SNP would have a separation of a plurality of nucleotides (the insertion in addition to the SNP). The artisan would be motivated as Daly suggest the detection of insertions. The artisan would have a reasonable expectation of success as the artisan is using known probes by known methods.

Response to Arguments

This is a new grounds of rejection necessitated by amendment.

10. Claim 1, 3-4, 68-69 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Akhras et al (PLOS one (2007) volume 2 (9) e915 and supplemental table) (IDS 3/28/2013), Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side the target region in the nucleic acid, wherein the MIPs capture at least the target region, and, wherein some MIPs in the probe set capture additional flanking sequence of various lengths." The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Akhras teaches, "The Connector Inversion Probe (CIPer) reaction (Figure 1) shares some basic design features with a recently described assay, the PathogenMip assay

[17], which includes: i) probe hybridization, single "G" base gap fill and probe circularization, ii) exonuclease based circular DNA selection, iii) probe inversion by relinearization, and iv) universal PCR amplification. The distinguishing and key feature of the CIPer method is a modified first reaction step involving a complete filling of an extensive gap formed by the probe and target (Figure 1B). The 39end of the probe, which we call the Extension Site (ES), primes for polymerization, while the 59end serves as point of ligation and is referred to as the Anchor Site (AS) (Figure 1). With all four dNTPs present, the polymerase is capable of extending past the intended point of ligation, generating a false negative. To address this problem, probes were designed to have an annealing temperature of approximately 5 degrees higher for the AS than that of the ES. The AS therefore blocks DNA extension when using a polymerase deficient in strand displacement at an appropriate intermediate temperature (50uC). For enhanced sensitivity and specificity a vast variety of probe concentrations and thermoprofiles were explored. Probes used in the 10–100 fmol concentration range yielded the strongest signal. Higher cycle numbers and shorter annealing times created a more efficient thermoprofile. The CIPer method successfully genotyped 1 pg of plasmid DNA in the presence of 200 ng non-reacting human genomic DNA, without generating any false positives (Figure S1). Assay optimizations were based on genotyping of HPV plasmid 56, validated by either SYBR GREEN assay or agarose gel electrophoresis, followed by Pyrosequencing verification (see Results, The Conserved Sequence Primer Connector Inversion Probe (CSP-CIPer))."

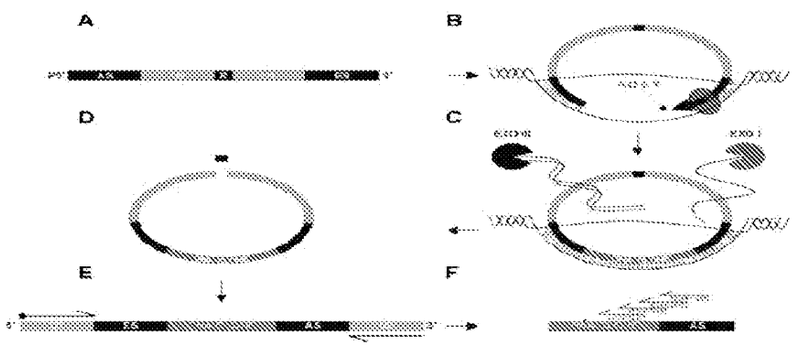


Figure 1. Schematic overview of Connector Inversion Probe (CIPer) technology. A) Synthetic oligonucleotide containing regions *i AS and ES* (anchor site and extension sites; approximately 20 base pair fragments homologous to regions flanking target of interest. ii) *R*: restriction site for probe linearization; iii) *U1 and U2*: universal primer regions for inverted probe amplification. B) Target rescue through complete gap filling by a DNA polymerase and ligation-based probe circularization. C) Circular DNA enrichment through degradation of linear DNA by enzymes Exonuclease I and III, which are deactivated prior to the next step. D) Probe linearization by restriction site cleavage. E) Inverted probes are amplified with universal primers; one is biotinylated for subsequent amplicon validation. F) Amplicon validation using multiple sequencing primers.
doi:10.1371/journal.pone.0009915.g001

, Akhras teaches, "CIPer detection was also applied to screening of resistance mutations in Neisseria gonorrhoeae. Two CIPers were used to perform a duplex amplification in a single-tube of the genes gyrA and parC [23], which are known to mutate easily and by specific SNPs generate resistance to ciprofloxacin and other quinolone antibiotics. The CIPers were designed with CIP creator 1.0.1 (http://bioel.stanford.edu/CIPer) based on previously described PCR primer-pairs not originally intended for multiplex PCR [21]. We intentionally inverted the gyrA CIPer to target the negative strand, while the parC CIPer targeted the positive strand, to illustrate that CIPers can be used on both DNA strands. In the case of close target proximities, it might be wise to revise such a strategy. Mutations on amino acid residues S91 and D95 for gyrA, and E91 for parC were the particular subjects of our interrogation. There are many other candidate genes for future CIPer-based epidemiological studies of antibiotic resistance [31]."

Thus Akhras teaches providing a sample comprising a target nucleic acid (DNA clone), contacting the sample with a plurality of probes that flank two different resistance

mutations in two different Neisseria gonorrhoeae genes of the Neisseria gonorrhoeae chromosome that do not overlap in the 5' region and the 3' region, converting the hybridized probe to a plurality of circularized probes comprising the target sequences, isolating the probes and sequencing the target nucleic acids.

Arkhas does not specifically teach the use of MIPs in which one MIP provides additional flanking sequences of the target region.

However, Blasczyk teaches, "Even if sequencing is performed in both directions, the ends of the templates will not yield readable sequencing ladders. Indeed, these problems can be solved by the use of 5' and 3' nested sequencing primers." (page 102 last paragraph-top of page 103).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to design MIPs to have 5' and 3' targeting arms hybridize to the sequence immediately adjacent to the target region and a MIPs to either hybridize either completely 5' and 3' of the target arms or partially overlapping the 5' and 3' targeting arms. The artisan would be motivated to identify and/or detect mutations or SNPs in the targeting arms which do not affect the ability of the targeting arms of the most internal MIP to hybridize. The artisan would have a reasonable expectation of success as the artisan is merely using the idea of nest sequencing to design the MIPs and improve the quality and amount of data obtained.

With regards to claim 69, Arkhas teaches 100bp target (figure 2).

Response to Arguments

This is a new grounds of rejection in view of the amendment.

.

Summary

No claims are allowed.

Conclusion

11. 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 https://ppair-my.uspto.gov/pair/PrivatePair. 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. 13/266,862	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					
	B					
	C					
	D					
	E					
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	I					
	J					
	K					
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	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	Daly (Clinical Chemistry (2007)volume 53, pages 1222-1230)
	V	Hardenbohl (Genome Research (2005) volume 15, pages 269-275)
	W	Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110)
	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., EX1002, p. 1873

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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

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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)	2021-01-14
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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	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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/SP/	1	5434049	A	1995-07-18	Okano et al.	
/SP/	2	5491224	A	1996-02-13	Bittner et al.	
/SP/	3	6020127	A	2000-02-01	MacKenzie et al.	
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/SP/	8	10604799		2020-03-31	Porreca et al.	

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	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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/SP/	1	2716766	EP	A1	2014-04-09	Berry Genomics Co., Ltd		
/SP/	2	1996/019586	WO	A1	1996-06-27	Visible Genetics Inc		
/SP/	3	2006/084132	WO	A2	2006-08-10	Agencourt Bioscience Corp		
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/SP/	5	2007/123744	WO	A2	2007-11-01	Solexa, Inc		
/SP/	6	2009/076238	WO	A2	2009-06-18	Complete Genomics, Inc		

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	Art Unit	1634
	Examiner Name	S. C. Pohnert
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/SP/	7	2010/115154	WO	A1	2010-10-07	Fluidigm Corp		
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/SP/	19	2015/119941	WO	A2	2015-08-13	Igenomx Internat Genomics Corp		

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EFS ID:	43355763
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	27-JUL-2021
Filing Date:	13-MAR-2012
Time Stamp:	18:55:24
Application Type:	U.S. National Stage under 35 USC 371

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-002-01US-Response-7-27-21.pdf	408130 a8619a73b83818a88580797354ea39897c3e2178	yes	14

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	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
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Attorney Docket No. MLB-002/01US 34468/8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
APPL. NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

Commissioner for Patents
P.O. Box 1450
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RESPONSE

This paper is in response to the non-final Office Action mailed April 27, 2021, from the United States Patent and Trademark Office.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

Applicant submits that no fees are due with this response. Nevertheless, application authorizes the Commissioner to charge any required fee to Deposit Account No. 50-0369.

Amendments to the Claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently amended) A method for analyzing a target nucleic acid, the method comprising:

providing a sample comprising nucleic acid comprising a target region;

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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region ~~sequence of various lengths~~;

converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target and some comprising the additional flanking nucleic acids ~~sequences of various lengths~~;

isolating the plurality of circularized probes; and

analyzing the target region.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

4. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, different than the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

Petitioner Illumina, Inc., EX1002, p. 1888

5-67. (Canceled)

68. (Previously Presented) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized on either side of the target region, are separated by a plurality of nucleotides on the nucleic acid.

69. (Previously Presented) The method of claim 1, wherein the target region comprises at least 50 base pairs of DNA.

70. (New) The method of claim 1, wherein each target region is captured by at least three different MIPs.

71. (New) The method of claim 70, wherein the step of analyzing the target region comprises sequencing the copy of the target and the additional flanking nucleic acids to generate sequence reads.

72. (New) The method of claim 71, wherein the sequencing is next generation sequencing.

73. (New) The method of claim 72, wherein the step of analyzing comprises averaging sequence reads from the at least three different MIPs.

Petitioner Illumina, Inc., EX1002, p. 1889

Remarks

Claims 1, 3, 4, and 68-69 are pending in the application, with claim 1 being the only independent claim. Claim 1 is amended for the purpose of clarity and to address the rejections under 35 U.S.C. §112 detailed below. New claims 70-73 are added. Support for the claim amendments and new claims can be found throughout the as-filed application, for example at page 33, lines 30-32; page 34, lines 9-15; page 35, line 24 to page 36, line 5; page 36, lines 9-23; page 37, lines 19-23; and Figure 2 and Figure 3.

No new matter is added.

Rejections under 35 U.S.C. §112, first paragraph

The Office Action, at pages 4-5, rejected claims 1, 3-4, and 68-69 under 35 U.S.C. §112, first paragraph, as lacking written description.

Applicant submits that the pending claims are expressly supported by the application as-filed.

When analyzing written description, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, that the applicant was in possession of the invention as now claimed. *See, Vas-Cath, Inc.*, 935 F.2d at 1563-64; s*ee also MPEP §2163(I)(B).* "While there is no *in haec verba* requirement, newly added claims or claim limitations must be supported in the specification through express, implicit, or inherent disclosure." *MPEP §2163(I)(B).*

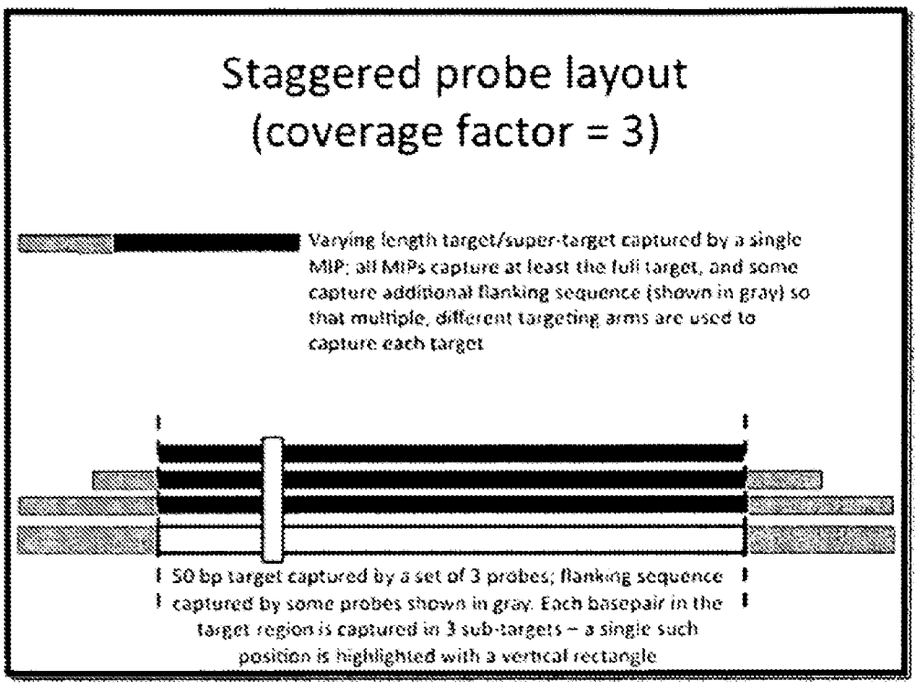
The pending claims recite contacting a sample with a probe set comprising a plurality of different MIPs for each target region, in which each MIP captures the target region and some MIPs also capture additional nucleic acids flanking the target region. The claims are fully supported by the specification in discussing a staggered probe approach, for example at pages 32-38, under the header "*1. Reducing representational bias in multiplex amplification reactions:.*" Specific support for these elements of the claims are detailed in the table below:

Petitioner Illumina, Inc., EX1002, p. 1890

Claim 1	**Support in as-filed specification of U.S. Serial No. 13/266,862**
1. A method for analyzing a target nucleic acid, the method comprising: providing a sample comprising nucleic acid comprising a target region;	"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)." *Page 32, lines 24-28.*
contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes (MIPs),	"In some aspects, the disclosure provides probe sets that comprise a plurality of different probes. . . An exemplary probe is a molecular inversion probe (MIP)." *Page 33, lines 10-14*
each MIP comprising a 5' targeting arm, a central region, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize on either side of the target region in the nucleic acid,	"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." *Page 33, lines 11-14.*
wherein the targeting arms of each MIP hybridize on either side of the target region in the nucleic acid,, wherein each of the MIPs capture at least the target region, and, wherein some of the MIPs in the probe set capture additional nucleic acids flanking the target region;	"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." *Page 36, lines 17-23*

Additional support for the claims is provided by Figures 2 and 3 of the as-filed application, reproduced below:

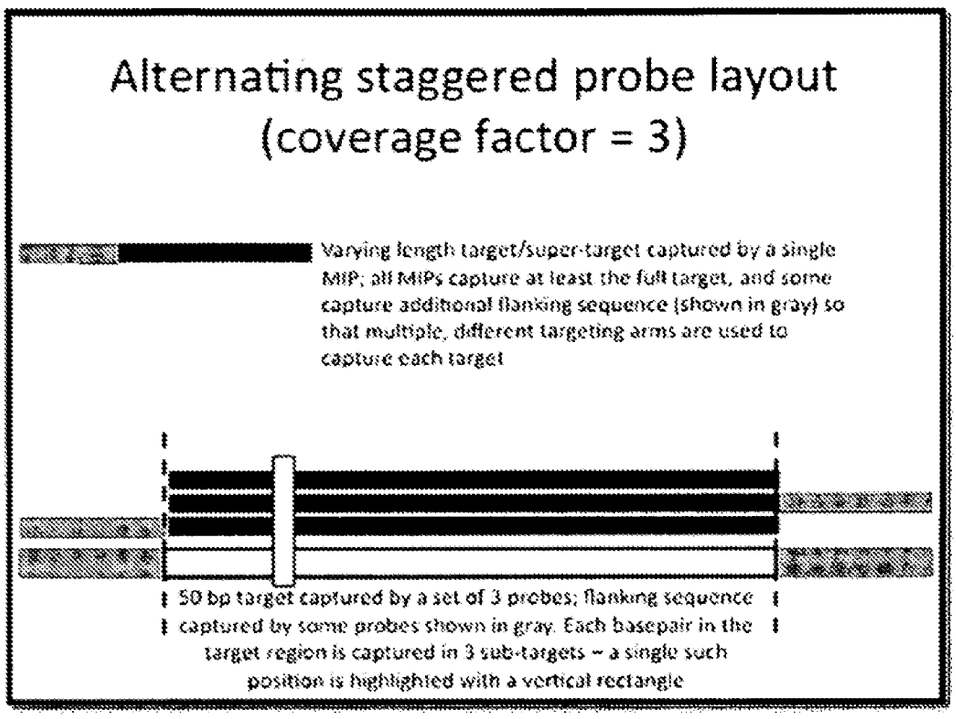
Figure 2



As depicted, the top-most MIP captures the target region without capturing any additional flanking nucleic acids. A second MIP, immediately below the top-most MIP, captures the entire target region and a portion of flanking nucleic acids on each end, of the target region, shown in gray. A third MIP, immediately below the second MIP, captures the entire target region and a lengthier portion of flanking nucleic acids on both ends in comparison to the second MIP.

Figure 3 shows another embodiment of a staggered probe the claimed invention.

Figure 3



The top-most MIP captures the target region without capturing any additional flanking nucleic acids. A second MIP, immediately below the top-most MIP, captures the entire target region and flanking nucleic acids on one end of the target sequence, shown in gray. A third MIP, immediately below the second MIP, captures the entire target region and a portion of the flanking nucleic acids on the opposite end of the target region in relation to the second MIP.

Applicant submits that even a cursory review of the Specification makes it clear that the pending claims are expressly supported by the application as-filed. Accordingly, applicant submits that the rejections under 35 U.S.C. §112, first paragraph, have been overcome.

Additionally, the Office Action, on page 4, stated that Claim 1 "is functionally claiming how the MIPs relate to the flanking sequences, but provide no specific limitations or structure for the probes." Applicant submits that a person having ordinary skill in the art would understand the structure of the MIPs claimed that capture a target region and flanking nucleic acids. Specifically, each MIP is an oligonucleotide comprising a 5' targeting arm, a central region, and

a 3' targeting arm. The 5' targeting arm and 3' targeting arm each have a specific sequence of nucleotides that are the reverse compliment of a sequence located upstream and downstream of a target region, and through circularization, described in detail on page 22 of the application, capture the sequence of nucleic acids between the two targeting arms. A person of ordinary skill in the art would understand that where a targeting arm binds upstream or downstream of the target region and also upstream or downstream of nucleic acids flanking the target region, those nucleic acids flanking the target region would also be captured by the MIP. Therefore, the claims provide a structure to the MIPs and are not functional, but rather the structure of the MIPs provide their function.

Accordingly, applicant further submits that the structure of the MIPs claimed would be clear to a person having ordinary skill in the art in accordance with 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph

The Office Action, at pages 5-6, rejected claims 1, 3-4, and 68-69 under 35 U.S.C. §112, second paragraph, as lacking as being indefinite. Specifically, the Office Action states that "the only recitation of various is with to example 5 which indicates the various lengths is dependent on the target sequence, not the targeting arms. Thus, it is unclear how the wherein clause provides structure for the MIP."

The Office Action is incorrect. The wherein clause, and the claim as a whole does provide structure for the MIP. The application discusses in detail the MIPs recited by the claimed invention, for example in discussing a staggered approach to MIP capture.

The Federal Circuit has ruled, that in analyzing indefiniteness, "if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more." *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624 (Fed.

Cir. 1985).

Applicant submits that pages 35-37, Figure 2, and Figure 3, all detail the staggered approach recited by the instant claims. Specifically, pages 35-36 of the application discuss Figures 2 and 3 (each reproduced above), that detail two separate embodiments of a staggered approach. The specification discloses that "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 difference sequence." *As-filed application at page 35, lines 25-27 and 33 to page 36, line 2.* The MIPs are able to accomplish this because "Targeting arms land immediately adjacent to the black or gray regions shown." *Id. at page 35, lines 29-30 and page 36, lines 4-5.*

Using Figures 2 and 3 as an example, Applicant submits that a person having ordinary skill in the art in view of the specification, would understand how the 5' targeting arm, central region, and 3' targeting arm of each MIP would be designed to enable the targeting arms of each MIP to hybridize on either side of the target region (black) and also any flanking nucleic acids (gray), thereby capturing both the target region and the flanking nucleic acids.

Those passages satisfy the standard set forth in *Shatterproof Glass.* 758 F.2d at 624. Applicant submits that any fair reading of the application makes clear that Applicant has provided substantial guidance and detail regarding the claimed invention involving the capture of flanking sequences together with a target sequence.

Accordingly, applicant submits that the rejections under 35 U.S.C. §112, second paragraph, have been overcome.

Rejections under 35 U.S.C. §103(a)

The Office Action, at pages 6-10, rejected claims 1 and 68 under 35 U.S.C. §103(a) over Daly (Clinical Chemistry, 2007, volume 53, pages 1222-1230) in view of Hardenbohl (Genome Research, 2005, volume 14, pages 269-275).

The Office Action, at pages 10-14, rejected claims 1, 3-4, and 68-69 under 35 U.S.C.

§103 over Akhras, et al., (PLOS one, 2007, 2(9):e915 and supplemental table) and Blasczyk (Tissue Antigens, 1996, volume 47, pages 102-110).

Applicant submits that each of the claims include elements that cannot be found anywhere in the cited references. Absent disclosure of the missing elements, Applicant submits that there can be no prima facie case for obviousness.

In general, the Patent Office must establish three basic criteria in order to establish a prima facie case of obviousness. There must be a suggestion to modify a reference or to combine references to lead one of ordinary skill in the art to the claimed invention; the cited references must convey a reasonable expectation of success in arriving at the claimed invention; and the suggestion to modify the references must be found in the prior art, not in the applicant's disclosure. *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991). An obviousness rejection cannot be established in the first place unless each claim element is disclosed in the cited art. *In re Royka,* 490 F.2d 981 (CCPA 1974). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 220 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 851 (1984). The Federal Circuit has made clear that "while 'common sense' can be invoked, even potentially to supply a limitation missing from the prior art, it must still be supported by evidence and a reasoned explanation . . . [T]his is particularly true where the missing limitation goes to the heart of an invention." *Arendi v. Apple*, 832 F.3d 1355, 1363 (Fed. Cir. 2016).

None of the cited references disclose sets of MIPs in which different MIPs capture the same target region. The cited references also fail to disclose sets of MIPs in which some of the MIPs capture nucleic acids flanking a target. The Office has not produced a single reference that shows either of those two elements of the invention.

Daly and Hardenbohl

Neither Daly nor Hardenbohl disclose sets of MIPs in which different MIPs capture the

same target region or MIPs in which some of the MIPs capture nucleic acids flanking a target.

Daly reports the use of MIPs in an assay of 1227 variants in 169 genes. *Daly, at page 1223.* Daly does not report the use of different MIPs to capture the same target region.

Rather, Daly reports that "MIPs are designed to be locus-specific rather than allele-specific and require only a single probe per marker, so any loss of performance of a probe will affect both alleles equally, avoiding unbalanced genotyping." *Id.* Daly reports that "a single best probe design for each locus," was chosen with only "a single probe for each variant." *Id., at 1224.*

Not only does Daly NOT report the use of multiple different probes for any given target region, Daly explicitly teaches away from contacting a single target region with different MIPs by expressly requiring only a single probe per marker. Daly is also entirely silent about MIPs that would capture a target region and additional flanking nucleic acids.

Hardenbohl also does not disclose sets of MIPs in which different MIPs capture the same target region or MIPs in which some of the MIPs capture nucleic acids flanking a target.

Hardenbohl cannot remedy the deficiencies of Daly, because Hardenbohl suffers from the very same deficits. Hardenbohl reports methods for the closed circularization, isolation, and analysis of MIPs. Like Daly, Hardenbohl reports using "only a single probe per SNP." *Hardenbohl, at page 272.* Additionally, like Daly, nowhere does Hardenbohl report any MIP that would capture the target region and additional flanking nucleic acids.

This is because Daly and Hardenbohl represent the specific prior art that the as-filed specification makes clear cannot achieve large uniformity or highly reproducible capture/amplification efficiency. *As-filed application at page 33, lines 16-20.* By using only one single probe per target region, neither Daly nor Hardenbohl cannot possibly average out error and bias, as provided by the sets of MIPs of the recited claims. *Id., at lines 27-29; see also New Claim 73.*

Applicant notes that the Office Action, at page 8, acknowledges that Daly does not teach

probes that capture flanking regions. The Office Action does not, and could not reasonably, assert that Hardenbohl provides this element. Rather, the Office Action, at page 9, states that an artisan would be motivated to modify Daly provide a MIP that captures additional flanking sequences. However, the Action provides no evidence as to why that would be the case.

The Office Action's reliance on a single prior-art reference as providing a limitation that the Office Action itself acknowledges the reference does not report, is an improper rejection under 35 U.S.C. §103. The Office Action has not provided evidence or a reasoned explanation as to why an artisan would be motivated to modify Daly to provide a missing limitation, when neither the reference, nor the Office Action, provides any reason or benefit in doing so.

Akhras and Blasczyk

Like Daly and Hardenbohl, neither Akhras nor Blasczyk discloses sets of MIPs in which different MIPs capture the same target region or MIPs in which some of the MIPs capture nucleic acids flanking a target.

Akhras reports Connector Inversion Probes (CIPers) that bind to regions flanking a target, and that then are circularized to enrich the target DNA. *Id., at FIG. 1.* Akhras reports a single probe for the detection of each of 24 different clinically relevant HPV genotypes. *Id., at abstract.* Akhras provides the full sequence of each probe used to detect each genotype, and not a single genotype was assayed using two different probes. *Akhras at page 9, Table 3.* Only a single probe was used for every target. *Id.*

Blasczyk makes no mention of MIPs at all.

Blasczyk reports only the improvements to PCR products to overcome the limitations of Sanger sequencing. *Blasczyk, at page 102-103.* Even in seeking to improve PCR products, and in contrast to the interpretation of Blasczyk provided in the Office Action, Blasczyk teaches away from even using multiple primers for the same target. Specifically, Blasczyk clarifies that "the use of a nested approach requires the stocking of large amounts of sequencing primers. Hence,

the application of dye primer sequencing techniques becomes infeasible." *Id. at 103.* Blasczyk not only demands the use of a single primer for any given location, but reports that the use of multiple primers per target would be infeasible. This is an explicit teaching away from the claimed invention. Even in mentioning a nested approach, Blasczyk makes no mention of amplifying of sequences flanking a target, but only amplification of products to provide better sequencing of the first 10-15 bases of the amplification product. *Id.*

Applicant notes that the Office Action, at page 14, acknowledges that Akhras does not teach the use of MIPs in which some MIPs capture additional nucleic acids flanking the target region. Blascyk clearly cannot remedy that deficiency.

The references together rebut any assertion that the use of multiple different probes for a single target region would be obvious to a person having skill in the art. As quoted above, Daly explicitly teaches away from the use of multiple probes to assay a single target. Insofar as Blaczyk can even be considered in any way relevant to MIP capture (which it is not), Blaczyk explicitly teaches away from nested approaches to primer design, believing such approaches to be "infeasible". *Blasczyk, at page 103.* The references are also entirely silent as to the capture of nucleic acids flanking a target region, a second element of the pending claims.

The cited references provided by the Office's search serve to further emphasize that the claimed methods are non-obvious and should be allowed.

In view of the above remarks, Applicant believes that the rejections under section 103 are overcome.

Conclusion

Applicant respectfully submits that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: July 27, 2021

Respectfully submitted,
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63876931 v1

Petitioner Illumina, Inc., EX1002, p. 1900

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8	6082

21710 7590 09/27/2021

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
09/27/2021	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

Office Action Summary	**Application No.** 13/266,862	**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 7/27/2021.

☐ 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) 1,3-4 and 68-73 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) 1,3-4 and 68-73 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 4/8/2021 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., EX1002, p. 1902

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. 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 7/27/2021.

Claims 1, 3-4,68-73 are pending.

Claims 2, 5-67 have been canceled.

Claim 69 has been added by amendment.

Claim 1 has been identified as amended.

Claims 1, 3-4 and 68-73 are being examined.

Any rejection or objection not reproduced below has been withdrawn upon further consideration.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Claim Rejections - 35 USC § 112

2. 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.

3. Claims 71 is 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 applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

Claim 71 has been amended to recite, "wherein the step of analyzing comprises averaging sequence reads from the at least three different MIPs." The metes and bound are unclear as to what is being averaged of the sequence reads size, base composition, number of nucleotides, etc. This rejection can be overcome by amending the claim to identify what is being averaged about the sequencing reads.

Response to Arguments

This is a new ground of rejection.

Claim Rejections - 35 USC § 103

4. 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.

5. Claim 1, 68, 70-71 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Daly (Clinical Chemistry (2007)volume 53, pages 1222-1230) and Hardenbohl (Genome Research (2005) volume 15, pages 269-275).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in

an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable

interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of different MIPs encompasses multiple copies of a MIP, each one being different from the other copies.

Daly teaches, " Molecular inversion probe (MIP) technology is an oligonucleotide-based method that can be used to analyze several thousand SNPs in a single assay (20). This technique has been used extensively for the HapMap project (21) and offers several advantages for multiplex genotyping. First, PCR amplification occurs after mutation detection, at which time MIPs have been converted to standard-length oligonucleotides of similar sequence composition utilizing common PCR primers. Second, the MIPs are designed to be locus-specific rather than allele specific and require only a single probe per marker, so any loss of performance of a probe will affect both alleles equally, avoiding unbalanced genotyping. Third, each probe has two recognition sequences as in PCR but retains unimolecular hybridization kinetics, enabling high multiplexing with low concentration requirements. Finally, the use of molecular tag sequences on the probes allows hybridization to the microarray to be independent of the gene sequence, increasing the specificity and sensitivity of detection and allowing for a high degree of flexibility in assay design (22)." (page 1223, 1st column top).

Daly continues, " We have applied MIP technology to develop an assay testing 1227 variants in 169 genes involved in drug metabolism. Within this set, we have chosen a core set of 165 variants in 27 genes for extensive analytical validation." (page 1223, 1st column, 2nd full paragraph).

Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

Daly does not teach the sequence of the probes or specifically teach probes with additional flanking region.

However, it would have been prima facie oblivious to one of ordinary skill in the art at the time the invention was made a MIP to detect a SNP (target region) that detected an insertion would provide additional flanking sequence relative to a probe capturing the target sequence without an insertion. The artisan would be motivated as Daly specifically teaches detection of SNPs and insertions and deletions. The artisan would have a reasonable expectation of success as the artisan is merely designing known probes.

Daly does not specifically converting to a closed circularized probe , isolating and analyzing.

However, Daly in the first cited paragraph references Hardenbohl (reference 20).

Hardenbohl teaches., "single oligonucleotide probe with recognition sequences at each terminus is hybridized with a genomic target sequence such that it forms a circular structure, with the ends of the probe abutting. This leaves a single base gap at the location of a SNP. This gapped-duplex is then tested in four separate reactions, each

with a single dNTP species present, in which successful polymerization/ligation provides allelic differentiation. The probes are subsequently released from the genomic DNA and those that have been covalently circularized in the correct allele/nucleotide reaction combinations are amplified using a "universal" PCR primer pair. Each amplified probe contains a unique tag sequence that is complementary to a sequence on the universal tag array. Tags have been selected to have a similar Tm and base composition and to be maximally orthogonal in sequence complementarity. Amplicons are fluorescently labeled and the tag sequences released from the genome homology regions using a restriction endonuclease treatment. The tags are then detected using a complementary tag array." (MIP technology, page 270).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to circularize, isolate and analyze the MIP and target region. The artisan would be motivated as Daly specifically references Hardenbohl. The artisan would have a reasonable expectation of success as the artisan is using art accepted probes in an art accepted manner.

With regards to claim 68, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that the detection of an insertion by a probe designed to detect a SNP would have a separation of a plurality of nucleotides (the insertion in addition to the SNP). The artisan would be motivated as Daly suggest the detection of insertions. The artisan would have a reasonable expectation of success as the artisan is using known probes by known methods.

With regards to claim 70, Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the

chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

With regards to claim 71, Hardenbohl teaches sequencing (674, 2nd column-675). Daly teaches sequencing (figure 1A).

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

The response continues by asserting the Day teaches away from multiple probes as the response asserts Daly teaches the use of a single probe for each locus. This argument has been thoroughly reviewed but is not considered persuasive as Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

The response continues by asserting that Hardenbohl does not correct the deficiencies. This argument is not persuasive for the reasons of record.

6. Claim 1, 3-4, 68-71 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable

interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of different MIPs encompasses multiple copies of a MIP, each one being different from the other copies.

Krishnakumar teaches, "As a proof of principle, we used SMART technology to simultaneously amplify 485 human exons ranging from 100 to 500 bp from human genomic DNA. In multiple repetitions, >90% of the targets were successfully amplified with a high degree of uniformity, with 70% of targets falling within a 10-fold range and all products falling within a 100-fold range of each other in abundance. We used long padlock probes (LPPs) >300 bases in length for the assay, and the increased length of these probes allowed for the capture of human sequences up to 500 bp in length, which is optimal for capturing most human exons. To engineer the LPPs, we developed a method that generates ssDNA molecules with precise ends, using an appropriately designed dsDNA template. The template has appropriate restriction sites engineered into it that can be digested to generate nucleotide overhangs that are suitable for lambda exonuclease digestion, producing a single stranded probe from dsDNA. The SMART technology is flexible and can be easily adapted to multiplex tens of thousands of target sequences in a single reaction.."

Krishnakumar teaches, " In a series of singleplex assays, padlock probes that were 120 bases in length were annealed to human DNA, and the gap-fill reaction was performed as described in Materials and Methods using the conditions for the Stoffel DNA polymerase. After completion of the gap-fill reaction with the formation of the circular DNA molecule by ligation, the desired DNA sequences were amplified using

common primers flanking the 3' and 5' target sequences of the padlock probe (Fig. 1D). We measured the performance of the assay by running the amplified products on a 2% agarose gel to determine the length of the amplified products. We concluded that the assay was successful and quite reproducible when the length of gap-fill sequences was 200 bases, but we found that the consistency and the reproducibility of the assay diminished as the size of the gap-fill region increased [supporting information (SI) Tables S1 and S2]."

Krishnakumar continues, "To test whether short padlock probes were limiting the gap-fill reaction, we needed to make longer probes. To this end, we developed a methodology for making probes that were 300 bases. We posited that the LPPs should (potentially) overcome the limitations of the smaller-size probes. In our current protocol, the ssDNA probe is produced from a specifically designed dsDNA template using a series of enzymatic reactions and selective removal of one of the strands using lambda exonuclease digestion. We first built the ''core'' construct of the template that is common to all probes. The core is composed of a common nucleic acid sequence, the spacer, derived from the bacteriophage lambda flanked by the amplification primers (Fig. 1A)."(page 9297, last paragraph).

While Krishnakumar teaches padlock probes (MIPs) to detect different size target sequences, Krishnakumar does not specifically teach the use of MIPs in which one MIP provides additional flanking sequences of the target region.

However, Blasczyk teaches, "Even if sequencing is performed in both directions,

the ends of the templates will not yield readable sequencing ladders. Indeed, these problems can be solved by the use of 5' and 3' nested sequencing primers." (page 102 last paragraph-top of page 103).

Kotsch teaches, "The use of nested sequencing primers additionally increased the specificity and quality of the sequencing reactions." (495, 2ND column, bottom)

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to design MIPs to have 5' and 3' targeting arms hybridize to the sequence immediately adjacent to the target region and a MIPs to larger fragments encompassing the target region. The artisan would be motivated to identify and/or detect mutations or SNPs in or near the targeting arms of the MIPs targeting only the target region which may not be detected in the smaller target region. Further the artisan would be motivated to detect additional flanking sequences to provide more data. The artisan would have a reasonable expectation of success as the artisan is merely using the idea of nest sequencing to design the MIPs and improve the quality and amount of data obtained.

With regards to claim 3-, It would have been prima facie obvious to one of skill in the art prior at the time the invention was made that design padlock probes to detect fragments of 500 nucleotides the 3' and 5' targeting arms would not overlap have different sequences than padlock probes for detection of 200 nucleotides. The artisan would be motivated to provide targeting arms that are long enough to target the 200 or 500 nucleotide sequence without the expense of making them extremely long.

With regards to claim 68-69, Krishnakumar teaches MIPS with 2580-500 nucleotides in target region (figure 2).

With regards to claim 70, Krishnakumar teaches the use of 50 attomoles of the probes. Thus Krishnakumar teaches at least 2 different MIPS

Response to Arguments

This is a new grounds of rejection necessitated by the amendment.

The response asserts that Blasczyk teaches away on page 103. This argument has been thoroughly reviewed but is not considered persuasive as Blasczyk teaches, "However, the use of a nested approach requires the stocking of large amounts of sequencing primers. Hence, the application of dye primer sequencing techniques becomes infeasible." Thus the Blasczyk does not teach away from the use of MIPs that contain the target region and additional flanking sequences.

7. Claims 72-73 rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497) as applied to claim 1, 3-4, 68-71 above, and further in view of Chaisson (Bioinformatics (2004) volume 20, pages 2067-2074)

The teachings of Krishnakumar, Blasczyk, Kotsch are set forth above.

While Krishnakumar, Blasczyk, Kotsch teach sequencing of padlock probes (MIPs), they do not specifically teach next generation sequencing or averaging sequence reads from at least 3 MIPS.

However, Chaisson teaches fragment assembly for short reads including 454 Life Sciences sequencer ((2067, 2nd column, 1st paragraph).. Chaisson teaches the next generation sequencing allow for greater coverage at a lower cost than Sanger

sequencing. Chaisson teaches different methods of different read lengths (2067, 2nd column, 1st paragraph). Chaisson teaches determining average read length (page 2069, 2nd column bottom).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the arms of the MIPS and determine average read length. The artisan would be motivated to increasing the speed and coverage of sequencing while reducing the cost. The artisan would have a reasonable expectation of success as the artisan is using known methods of detecting sequences and determining average read length.

Response to Arguments

This is a new grounds of rejection necessitated by the amendment.

Summary

No claims are allowed.

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 https://ppair-my.uspto.gov/pair/PrivatePair. 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. 13/266,862	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					
	B					
	C					
	D					
	E					
	F					
	G					
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	I					
	J					
	K					
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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	Krishnakumar (Proceedings National Academy of Sciencies (2008) volume 105, pages 9296-9301)
	V	Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)
	W	Chaisson (Bionormatics (2004) volume 20, pages 2067-2074)
	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.

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Electronic Acknowledgement Receipt	
EFS ID:	44617620
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas C. Meyers/Aditya Ramanathan
Filer Authorized By:	Thomas C. Meyers
Attorney Docket Number:	MLB-002/01US 34468/8
Receipt Date:	27-DEC-2021
Filing Date:	13-MAR-2012
Time Stamp:	23:55:50
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1000
RAM confirmation Number	E2021BQN56052971
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-002-01US-Response-122721.pdf	162323 30d07d93083ee50f02579ef77990392bb6925edd	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment Submitted/Entered with Filing of CPA/RCE		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	10	
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	MLB-002-01US-RCE.pdf	697603 29d9e44a2f452a4368f0756db93987fe14029510	no	3
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	37833 bc149842ba377dabcb071a402909cdd5df5bff20	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	897759		

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-002/01US 34468/8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
APPL. NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

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

FILED ELECTRONICALLY

RESPONSE

This paper is in response to the final Office Action mailed September 27, 2021, from the United States Patent and Trademark Office.

Amendments to the Claims begin on page 2.

Remarks begin on page 4.

Applicant submits a Request for Continued Examination (RCE) with this response.

Applicant submits the fee for an RCE and authorizes the Commissioner to charge any other required fee to Deposit Account No. 50-0369.

Amendments to the Claims

This list of claims replaces all prior versions and listings of claims in this application.

1. (Currently amended) A method for analyzing a target nucleic acid, the method comprising:

providing a sample comprising nucleic acid comprising a target region;

contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes (MIPs) comprising different nucleotide sequences, each MIP comprising a 5' targeting arm, a central region, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region ;

converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target and some comprising the additional flanking nucleic acids;

isolating the plurality of circularized probes; and

analyzing the target region.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

4. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, different than the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

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5-67. (Canceled)

68. (Previously Presented) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized on either side of the target region, are separated by a plurality of nucleotides on the nucleic acid.

69. (Previously Presented) The method of claim 1, wherein the target region comprises at least 50 base pairs of DNA.

70. (Previously Presented) The method of claim 1, wherein each target region is captured by at least three different MIPs.

71. (Previously Presented) The method of claim 70, wherein the step of analyzing the target region comprises sequencing the copy of the target and the additional flanking nucleic acids to generate sequence reads.

72. (Previously Presented) The method of claim 71, wherein the sequencing is next generation sequencing.

73. (Currently amended) The method of claim 72, wherein the step of analyzing comprises averaging the nucleotide base-composition off the sequence reads from the at least three different MIPs.

Remarks

Claims 1, 3, 4, and 68-69 are pending in the application, with claim 1 being the only independent claim. Claim 1 is amended for the purpose of clarity and claim 73 is amended to address the rejection under 35 U.S.C. §112, second paragraph, discussed below. Support for the amendments to the claims can be found throughout the as-filed application, for example at page 33, lines 30-32; page 34, lines 9-15; page 35, line 24 to page 36, line 5; page 36, lines 9-23; page 37, lines 19-23; and Figure 2 and Figure 3.

No new matter is added.

Rejections under 35 U.S.C. §112, second paragraph

The Office Action, at pages 2-3, states that claim 71 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Office Action states that claim 71 recites "wherein the step of analyzing comprises average sequence reads from the at least three different MIPs" without reciting what is being averaged.

In response, applicant notes that claim 73, rather than claim 71, recites the language identified in the Office Action. Applicant has amended claim 73 to recite average the nucleotide base composition of the sequence reads.

In view of the amendment to the claims, applicant submits that the rejection under 35 U.S.C. §112, second paragraph, has been overcome.

2005

Rejections under 35 U.S.C. §103(a)

The Office Action, at pages 3-8, states that claims 1, 68, and 70-71 are rejected under 35 U.S.C. §103(a) over Daly (Clinical Chemistry, 2007, volume 53, pages 1222-1230) in view of Hardenbohl (Genome Research, 2005, volume 14, pages 269-275).

The Office Action, at pages 9-13, states that claims 1, 3-4, and 68-71 are rejected under

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35 U.S.C. §103(a) over Krishnakumar (Proceedings National Academy of Sciences, 2008, volume 105, pages 9296-9301), Blasczyk (Tissue Antigens, 1996, volume 47, pages 102-110), and Kotsch (Tissue Antigens, 1999, volume 52, pages 486-497).

The Office Action, at page 13, states that claims 72-73 are rejected under 35 U.S.C. §103(a) over Krishnakumar, Blasczyk, and Kotsch in further view of Chaisson (Bioinformatics, 2004, volume 10, pages 2067-2074).

None of the cited references disclose sets of MIPs in which MIPs comprising different nucleotide sequences capture the same target region. The cited references also fail to disclose sets of MIPs in which some of the MIPs capture nucleic acids flanking a target.

In general, the Patent Office must establish three basic criteria in order to establish a prima facie case of obviousness. There must be a suggestion to modify a reference or to combine references to lead one of ordinary skill in the art to the claimed invention; the cited references must convey a reasonable expectation of success in arriving at the claimed invention; and the suggestion to modify the references must be found in the prior art, not in the applicant's disclosure. *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991). An obviousness rejection cannot be established in the first place unless each claim element is disclosed in the cited art. *In re Royka,* 490 F.2d 981 (CCPA 1974). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 220 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 851 (1984). The Federal Circuit has made clear that "while 'common sense' can be invoked, even potentially to supply a limitation missing from the prior art, it must still be supported by evidence and a reasoned explanation . . . [T]his is particularly true where the missing limitation goes to the heart of an invention." *Arendi v. Apple*, 832 F.3d 1355, 1363 (Fed. Cir. 2016).

Because none of the cited references disclose sets of MIPs in which MIPs comprising different nucleotide sequences capture the same target region and also fail to disclose sets of MIPs in which some of the MIPs capture nucleic acids flanking a target, the Office Action has

not established a prima facie case of obviousness.

Daly and Hardenbohl

Neither Daly nor Hardenbohl disclose sets of MIPs in which different MIPs capture the same target region or MIPs in which some of the MIPs capture nucleic acids flanking a target.

Daly reports the use of MIPs in an assay of 1227 variants in 169 genes. *Daly, at page 1223.* Daly reports that "a single best probe design for each locus" was chosen with only "a single probe for each variant." *Id. at 1224 (emphasis added).* The MIP set was designed by synthesizing 641 probe designs, and the "single best probe design for each locus based on visual inspection of genotype cluster separation for each variant, as well as assay parameters such as call rate, repeatability, and trio accuracy" was selected. *Id.* Daly also reports that "[e]ach locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." *Id.* That is, each locus in Daly is assayed with three copies of the same MIP, each copy having an identical nucleic acid sequence.

Daly does not at all report the use of different MIPs with differing nucleic acid sequences to capture the same target region. Moreover, not only does Daly not report the use of multiple different probes for any given target region, Daly explicitly teaches away from contacting a single target region with different MIPs by expressly requiring only identical probes for any given locus. Daly is also entirely silent about MIPs that would capture a target region and additional flanking nucleic acids.

Hardenbohl also does not disclose sets of MIPs in which different MIPs capture the same target region or MIPs in which some of the MIPs capture nucleic acids flanking a target.

Hardenbohl cannot remedy the deficiencies of Daly, because Hardenbohl suffers from the very same deficits. Hardenbohl reports methods for the closed circularization, isolation, and analysis of MIPs. Like Daly, Hardenbohl reports using "only a single probe per SNP."

Hardenbohl, at page 272. Additionally, like Daly, nowhere does Hardenbohl report any MIP that would capture the target region and additional flanking nucleic acids.

Applicant notes that the Office Action, at page 8, states that because the probes of Daly "are on different portions of the microarray they are different." Although applicant does not agree with the Office Action's definition of "different" probes, Daly explicitly reports that the sequences of the probes on different location of the microarray are identical. Accordingly, Daly cannot report the step of contacting a sample with a sets of MIPs with different sequences capturing a single region

Krishnakumar, Blasczyk, Kotsch, and Chaisson

Like Daly and Hardenbohl, none of Krishnakumar, Blasczyk, Kotsch, or Chaisson discloses sets of MIPs in which MIPs comprising different nucleic acid sequences capture the same target region.

Krishnakumar reports the use of long padlock probes (LPPs) "that are three times larger" than probes in a "conventional MIP assay." *Krishnakumar at 9297.* Krishnakumar reports the use of 557 LPPs to assay 485 exons. *Id.* Within the 485 exons, the probes assayed "575 target sequences representing human exons present in 30 kinase genes." *Id. at 9299.* Accordingly, Krishnakumar provides only 557 probes to assay 575 targets. This requires that each probe in Krishnakumar assay a different target, with at least some LPPs assaying multiple identical targets.

Krishnakumar does not and cannot teach the use of multiple probes having different sequences that capture the same target.

Blasczyk makes no mention of MIPs or circularized probes at all.

Blasczyk reports only the improvements to PCR products to overcome the limitations of Sanger sequencing. *Blasczyk, at page 102-103.* Blasczyk reports the use of two additional primers to capture the 5' and 3' ends of a target nucleic acid, typically lost during Sanger

sequencing. The use of additional primers taught in Blasczyk, however, is limited to specific Sanger sequencing techniques. Blasczyk clarifies that "the use of a nested approach requires the stocking of large amounts of sequencing primers. Hence, the application of dye primer sequencing techniques becomes infeasible." *Id. at 103.* This is an explicit teaching away from the use of nested primers in any technique other than Sanger sequencing. Even in mentioning a nested approach, no single primer even captures the entire target region, with a first primer capturing the majority of the target region and the 3' and 5' primers each capturing only 10-15 bases at the ends of the target region. *Id.*

Kotsch too makes no mention of MIPs or circularized probes.

Moreover, Kotsch makes no mention of multiple different MIPs capturing a single target nucleic acid. Like Blasczyk, Kotsch seeks to overcome drawbacks in PCR-SBT strategies that "that do not allow sequence analysis of the 5' and 3' ends of the 2nd exon" in HLA-DRB genes. *Kotsch at 487.* Kotch reports the use of three nested primers that correspond to three variants of a conserved region in the 3' end of intron 1 of the HLA-DRB gene. *Id. at 488*. Because the 3' end of intron 1 of the HLA-DRB gene has limited diversity, at least one of the three primers of Kotch is likely to hybridize with the 3' end of intron 1 in order to then amplify exon 2. *Id. at 496.* Accordingly, Kotsch teaches only methods in which only a single primer is used to capture the target region and does not teach the use of multiple different primers that each capture a target region.

Chaisson also makes no mention of MIPS or any probes at all. Chaisson reports only that new computer-assisting assemblies may facilitate assembling short reads together, for example from pyrosequencing reads. *Chaisson at 2067-68.* Accordingly Chaisson cannot remedy the deficiencies of Krishnakumar, Blasczyk, or Kotsch.

Applicant notes that the Office Action, on page 13, states that Chiasson teaches methods of next generation sequencing. Applicant submits that Chaisson makes no mention of next generation sequencing and discusses the assembly of reads solely from 454 pyrosequencing. This

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is unsurprising given the 2004 publication date of Chiasson.

Summary

Altogether, the references together rebut any assertion that the use of multiple different probes comprising different nucleic acid sequences for a single target region would be obvious to a person having skill in the art. As quoted above, Daly explicitly teaches away from the use of multiple probes to assay a single target. This is because the cited art represents the specific prior art that the as-filed specification makes clear cannot achieve large uniformity or highly reproducible capture/amplification efficiency. *As-filed application at page 33, lines 16-20.* By using only single or multiple identical probes per target region, the cited art cannot average out error and bias, as provided by the claimed sets of MIPs with different sequences that capture a single region, as provided by the amended claims. *Id., at lines 27-29; see also New Claim 73.*

The cited references provided by the Office's search serve to further emphasize that the claimed methods are non-obvious and should be allowed.

In view of the above remarks, Applicant believes that the rejections under section 103 are overcome.

Conclusion

Applicant respectfully submits that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: December 27, 2021

Respectfully submitted,

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Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	13266862	Filing Date	2012-03-12	Docket Number (if applicable)	MLB-002/01US 34458/8	Art Unit	1634
First Named Inventor	Gregory Porreca			Examiner Name	Steven 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 _____

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

X Patent Practitioner Signature

Applicant Signature

EFS - Web 2.1.15

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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Signature of Registered U.S. Patent Practitioner			
Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2021-12-27
Name	Thomas C. Meyers	Registration Number	36989

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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:	13266862
Filing Date:	13-Mar-2012
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas C. Meyers/Aditya Ramanathan
Attorney Docket Number:	MLB-002/01US 34468/8
Filed as Small Entity	
Filing Fees for U.S. National Stage under 35 USC 371	

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($)
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	1000	1000
		Total in USD ($)		**1000**

Electronic Acknowledgement Receipt	
EFS ID:	44654624
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
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-002/01US 34468/8
Receipt Date:	03-JAN-2022
Filing Date:	13-MAR-2012
Time Stamp:	16:17:01
Application Type:	U.S. National Stage under 35 USC 371

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	Information Disclosure Statement (IDS) Form (SB08)	34468_8US_-_Information_Disclosure_Statement_Fillable_PDF.pdf	1037637 c06a7fb7a846107f3157f81d2fd729c0e833752f	no	8

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2	Non Patent Literature	Brinkman.pdf	1202568 90a57fba60a0ae15c8abec3cb65f1f9b8dfbbad6	no	11
Warnings:					
Information:					
3	Non Patent Literature	34468_8US_-_Chaisson.pdf	643654 17f5c8fa5cada1de72a80a3d5bf979909ccb977c	no	8
Warnings:					
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4	Non Patent Literature	Chennagiri-2013-ASHGmtg.pdf	156838 5f25b7a42361a22f3197ffe8c3744c47c38d9f22	no	2
Warnings:					
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5	Non Patent Literature	Chevreux-1999-ProcGCB.pdf	665185 ebb573b3007f33a9a5878d9dc2c6302487236d7f	no	13
Warnings:					
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6	Non Patent Literature	34468_24US_-_Chou-2010.pdf	1171199 4f64c947273c4ef18280e95b24ecf497eb33e5c5	no	11
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7	Non Patent Literature	Cremer.pdf	750689 e2e281b9585013ddad754d535ade9652348c473e	no	8
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8	Non Patent Literature	Cronin.pdf	1307789 0c3a11eb3009387f660adac8f5107aa876373b45	no	12
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9	Non Patent Literature	Deng-2012-NB.PDF	887689 ddf1bd81f62283cec7994909f52a9b43ed8a6737	no	12
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11	Non Patent Literature	Frey-2006-StatHacks.pdf	850589 c3b76c169810a3ac78ff7a13aee12d249cde397a	no	9
Warnings:					
Information:					
12	Non Patent Literature	34468_24US_-_Fu-2010.pdf	1002219 556f8ffda09ce48c0f7590dcb658476c78c338a5	no	12
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Information:					
13	Non Patent Literature	Goto-2010-Bioinform_.pdf	261554 9cfce92738b0b8d483d3f2051346d6aab78a2150	no	3
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14	Non Patent Literature	Guerrero-Fernandez-2013-Granada.pdf	406234 16b9f3afa920527b86036e6ce34af8bc21e04cea	no	8
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15	Non Patent Literature	34468_8US_-_Gupta-2014-JCI.pdf	623656 71e97a88d495f58e735a3784fcdf69a2468bb034	no	9
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16	Non Patent Literature	Gustincich-Biotechniques-1991.pdf	1830923 8c5c119be0616a6c03f74095dd8191ab6837b04d	no	4
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17	Non Patent Literature	Homer-2008-PLoSOne.pdf	1991422 17b50695884 91f0d29c6e15bfaf92bcb23e13ebf	no	9
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18	Non Patent Literature	34468_9US_-_Jares-2006.pdf	999697 86e2157dcf591d4753af7fc33c6e1e42fbb1390d	no	12
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19	Non Patent Literature	34468_9US_-_Johnson-2005.pdf	1083762 ee8db257bb60abceb9be0ef42ffbaa999cbf5d60	no	10
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Information:					
20	Non Patent Literature	29168_244US_-_Kambara-1988-BioTechnol_11.pdf	621210 2cf3332011ffb01f16b98f26009ec98f8564df35	no	6
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21	Non Patent Literature	Kennedy-2013-ASHGmtg.pdf	144805 68b3e8e0a071207ea92fa1e57e9ac0acfc670355	no	2
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23	Non Patent Literature	34468_8US_-_Krishnakumar.pdf	1060129 936176b6cd3e61092ae9cbe6900fbe694ec84697	no	6
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24	Non Patent Literature	Larkin-2007-Bioinformatics.pdf	353957 08b973bd020a1420163ba85cc80d3c4c77d495be	no	2
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25	Non Patent Literature	Lin-2008-Bioinformatics.pdf	662777 b3f645a0fe765463b471c5a0edd3a486989 40be6	no	7
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27	Non Patent Literature	McDonnell.pdf	60837 009fc900237fef2078faead37164854d2b87dc4b	no	1
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28	Non Patent Literature	34468_24US_-_Meyer-2008.pdf	1089249 535ac47dad6ac6b28a0b94779af9e281e305c26e	no	12
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30	Non Patent Literature	Moudrianakis-1965-PNAS.pdf	1325856 c72874d4ac699c7ee27daa5b6cf4374633703e0e	no	8
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Warnings:					
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32	Non Patent Literature	Sauro-How-Do-You-Calculate-2004.pdf	142346 00d24abbda607cafbde88c8c684a9713180199ef	no	3
Warnings:					
Information:					
33	Non Patent Literature	34468_40US_-_Schiffman-2007.pdf	232122 e3b26d5fbd932f4ff1ff24355e696adca57c8bae	no	5
Warnings:					
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Warnings:					
Information:					
35	Non Patent Literature	34468_24US_-_Sonnhammer-2002.pdf	219016 c26f03c583243cae803e43a3346ff32169d61d29	no	2
Warnings:					
Information:					
36	Non Patent Literature	Sunnucks-1996-Genetics.pdf	987812 3b48daeaf487176b50f7669baf23047fee123fcc	no	10
Warnings:					
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37	Non Patent Literature	34468_41US_-_Tarhini-2018.pdf	1585869 f16fab6beb881502fb09a3bfa44de028bbf6e890	no	11
Warnings:					
Information:					
38	Non Patent Literature	Tobler.pdf	937082 fcd02823c959c86e9ce617bf6c3a54d345874388	no	9
Warnings:					
Information:					
39	Non Patent Literature	34468_40US_-_Wang-2007.pdf	1048218 8fdcbcffcd52b00802003a86ebe1c3a81f5d766b	no	14
Warnings:					
Information:					
40	Non Patent Literature	WittungBiochemistry1997.pdf	640605 cacd6fb222e1df5c9893f66d11f7022200587b5e	no	7
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

CERTIFICATION STATEMENT

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

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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)	2022-01-03
Name/Print	Thomas C. Meyers	Registration Number	36,989

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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
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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	1	20040175719	A1	2004-09-09	Christians	
	2	20100227329	A1	2010-09-09	CUPPENS	
	3	20140274741	A1	2014-09-18	Hunter et al.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Gregory Porreca
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	1	Brinkman, 2004, Splice Variants as Cancer Biomarkers, Clin Biochem 37:584-594	
	2	Chaisson, 2004, Fragment assembly with short reads, Bionormatics, 20:2067-2074	
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	7	Cronin, 1996, Cystic Fibrosis Mutation Detection by Hybridization to Light-Generated DNA Probe Arrays" Human Mutation 7:244-255	
	8	Deng, 2012, Supplementary Material, Nature Biotechnology, S1-1 - S1-1 1, Retrieved from the Internet on 2012-10-24, 12 pages	

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	Attorney Docket Number	MLB-002/01US 34468/8

	9	Dou, 2012, Reference-free SNP calling: improved accuracy by preventing incorrect calls from repetitive genomic regions, Biology Direct 7:17	
	10	Frey, 2006, Statistics Hacks 108-115	
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	15	Gustincich, 1991, A fast method for high-quality genomic DNA extraction from whole human blood, BioTechniques 11 (3):298-302	
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	18	Johnson, 2005, Dark matter in the genome: evidence of widespread transcription detected by microarray tiling experiments, Trends in Genetics, 21(2):93-102	
	19	Kambara, 1988, Optimization of Parameters in a DNA Sequenator Using Fluorescence Detection, Nature Biotechnology 6:816-821	

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	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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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.

EFS Web 2.1.18

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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[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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8	6082

21710 7590 07/15/2022

BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
07/15/2022	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.** 13/266,862	**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 12/27/2021.

☐ 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) 1,3-4 and 68-73 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) 1,3-4 and 68-73 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 4/8/2021 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., EX1002, p. 1952

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. 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 12/27/2021 has been entered.

Claim Status and Formal matters

This action is in response to papers filed 12/27/2021.

Claims 1, 3-4,68-73 are pending.

Claims 2, 5-67 have been canceled.

Claim 1 and 73 have been identified as amended.

Claims 1, 3-4 and 68-73 are being examined.

Any rejection or objection not reproduced below has been withdrawn upon further consideration.

The previous 112 (b) has been withdrawn in view of the amendment.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application

61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Claim Rejections - 35 USC § 103

2. 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.

3. Claim 1, 68, 70-71 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Daly (Clinical Chemistry (2007)volume 53, pages 1222-1230), Hardenbohl (Genome Research (2005) volume 15, pages 269-275), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102).

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of capture is not defined by the specification. Thus the broadest reasonable interpretation is allowing hybridization or isolation (consistent with page 7-8 of the specification).

The prior art of record exemplifies that MIP and their analysis was known. MIPs with overlapping sequences were known, as were methods of tiling. Thus the claims are nothing more than the predictable combination of known steps and elements as exemplified below.

Daly teaches, " Molecular inversion probe (MIP) technology is an oligonucleotide-based method that can be used to analyze several thousand SNPs in a single assay (20). This technique has been used extensively for the HapMap project (21) and offers several advantages for multiplex genotyping. First, PCR amplification occurs after mutation detection, at which time MIPs have been converted to standard-length oligonucleotides of similar sequence composition utilizing common PCR primers. Second, the MIPs are designed to be locus-specific rather than allele specific and require only a single probe per marker, so any loss of performance of a probe will affect both alleles equally, avoiding unbalanced genotyping. Third, each probe has two recognition sequences as in PCR but retains unimolecular hybridization kinetics, enabling high multiplexing with low concentration requirements. Finally, the use of molecular tag sequences on the probes allows hybridization to the microarray to be independent of the gene sequence, increasing the specificity and sensitivity of detection and allowing for a high degree of flexibility in assay design (22)." (page 1223, 1st column top).

Daly continues, " We have applied MIP technology to develop an assay testing 1227 variants in 169 genes involved in drug metabolism. Within this set, we have chosen a core set of 165 variants in 27 genes for extensive analytical validation." (page 1223, 1st column, 2nd full paragraph).

Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

Daly does not teach the sequence of the probes or specifically teach probes with additional flanking region.

Nilsson teaches MIP, padlock probes and selector probes all are circularized by hybridization to target nucleic acids to target nucleic acids (Figure 1 and figure 2, throughout). Nilsson teaches the padlock probes use ligation, while MIPs and selector probes use gap filing and ligation (83, bottom 2nd column-85). Nilsson teaches the probes which are ligated are separated from non-closed probes by digestion (isolation). Nilsson in figure 3 demonstrates amplification of circularized probes. Nilsson teaches, "Currently, 12 000 MIPs can be amplified and analyzed in parallel. We expect that a similar, or greater, number of selector probes can be applied to amplify large sets of genomic DNA fragments for subsequent analysis using high-throughput sequencing technologies [24,25]. Much effort is being invested into developing low-cost sequencing

methods with the ultimate goal of sequencing an entire human genome for $1000 [5]. A more realistic goal, in the shorter term, is to sequence only the interesting parts of the genome, for example, all exons: the selector technology could be combined profitably with several of the sequencing techniques to achieve this." (bottom 1st column page 87, top of 2nd column).

Nilsson concludes, "Detailed understanding of multicellular organisms and many human diseases will ultimately require analyses of individual cells in their natural tissue environment."(page 87, 2nd column 1st full paragraph).

Thus Nilsson suggest examination of human nucleic acids samples by use of circular probes including padlock, MIP and selector probes which are circularized by hybridization, isolation, amplifying and sequencing to characterize disease states by the genetic status.

Nilsson does not specifically teach the use of overlapping probes or targeting overlapping sequences

Hardenbohl (Genome Research (2005) volume 15, pages 269-275) teaches, " Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

Chee et al (WO 95/11995) teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on

individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays to determine nucleic acid sequences (see Figure7 and page 37 line 10- page 38 line 34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and a target sequence for the identification of single base mutants possible in the reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (see page 18, lines 1-8). Chee teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-6). Chee teaches the probes are immobilized on an array. Chee teaches, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences' (page 32).

Johnson teaches, "The first genomic-scale study of transcription using microarrays was performed in Escherichia coli using probes 'tiled' at regular intervals (Box 1) to provide an unbiased view of transcription with respect to the locations of known and predicted genes [12"

Dong teaches methods and kits for amplification of target nucleic acids(abstract). Dong teaches the method before or in conjunction with sequencing (0115). Dong teaches some embodiments include amplification with ligase mediated amplification

techniques including padlock probes (0109). Dong in 0087 teaches, "In some embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both."

Mockler teaches the use of tiling arrays to examine the whole genome including overlapping and nonoverlaping (figure 1).

Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165)

Streit teaches the CFTR gene has multiple mutations in close proximity in exon 11 (table 2) (s549Nm G542X, G551D and R553X).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use overlapping circularized probes such as MIPs, padlock or selector probes using overlapping probes each have different nucleic acid arm sequences and thus capture additional flanking sequences. The artisan would be motivated to use to detect specific mutations as the art teaches MIPs that are overlapping and demonstrates the use of MIP to detect previously unknown transcripts.. The artisan would have a reasonable expectation of success as the artisan is merely designing and circularized probes such as MIPs, padlock or selector probes to detect known mutations by known means.

Daly does not specifically converting to a closed circularized probe , isolating and analyzing.

However, Daly in the first cited paragraph references Hardenbohl (reference 20).

Hardenbohl teaches., "single oligonucleotide probe with recognition sequences at each terminus is hybridized with a genomic target sequence such that it forms a circular structure, with the ends of the probe abutting. This leaves a single base gap at the location of a SNP. This gapped-duplex is then tested in four separate reactions, each with a single dNTP species present, in which successful polymerization/ligation provides allelic differentiation. The probes are subsequently released from the genomic DNA and those that have been covalently circularized in the correct allele/nucleotide reaction combinations are amplified using a "universal" PCR primer pair. Each amplified probe contains a unique tag sequence that is complementary to a sequence on the universal tag array. Tags have been selected to have a similar Tm and base composition and to be maximally orthogonal in sequence complementarity. Amplicons are fluorescently labeled and the tag sequences released from the genome homology regions using a restriction endonuclease treatment. The tags are then detected using a complementary tag array." (MIP technology, page 270).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to circularize, isolate and analyze the MIP and target region. The artisan would be motivated as Daly specifically references Hardenbohl. The artisan would have a reasonable expectation of success as the artisan is using art accepted probes in an art accepted manner.

With regards to claim 68, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that the detection of an insertion by a probe designed to detect a SNP would have a separation of a plurality of nucleotides (the insertion in addition to the SNP). The artisan would be motivated as

Daly suggest the detection of insertions. The artisan would have a reasonable expectation of success as the artisan is using known probes by known methods.

With regards to claim 70, Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

With regards to claim 71, Hardenbohl teaches sequencing (674, 2nd column-675). Daly teaches sequencing (figure 1A).

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims.

The response continues by asserting the Day teaches away from multiple probes as the response asserts Daly teaches the use of a single probe for each locus. This argument has been thoroughly reviewed but is not considered persuasive as the art as a whole demonstrates the use of tiling arrays to capture regions or targets of interest. Thus using MIPs that tile across a target of interest renders this limitation obvious.

The response continues by asserting that Hardenbohl does not correct the deficiencies. This argument is not persuasive for the reasons of record.

4. Claim 1, 3-4, 68-71 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Hardenbohl (Genome Research (2005) volume 15, pages 269-275) Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102)Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable

interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of capture is not defined by the specification. Thus the broadest reasonable interpretation is allowing hybridization or isolation (consistent with page 7-8 of the specification).

The prior art of record exemplifies that MIP and their analysis was known. MIPs with overlapping sequences were known, as were methods of tiling. Thus the claims

are nothing more than the predictable combination of known steps and elements as exemplified below.

Krishnakumar teaches, "As a proof of principle, we used SMART technology to simultaneously amplify 485 human exons ranging from 100 to 500 bp from human genomic DNA. In multiple repetitions, >90% of the targets were successfully amplified with a high degree of uniformity, with 70% of targets falling within a 10-fold range and all products falling within a 100-fold range of each other in abundance. We used long padlock probes (LPPs) >300 bases in length for the assay, and the increased length of these probes allowed for the capture of human sequences up to 500 bp in length, which is optimal for capturing most human exons. To engineer the LPPs, we developed a method that generates ssDNA molecules with precise ends, using an appropriately designed dsDNA template. The template has appropriate restriction sites engineered into it that can be digested to generate nucleotide overhangs that are suitable for lambda exonuclease digestion, producing a single stranded probe from dsDNA. The SMART technology is flexible and can be easily adapted to multiplex tens of thousands of target sequences in a single reaction.."

Krishnakumar teaches, " In a series of singleplex assays, padlock probes that were 120 bases in length were annealed to human DNA, and the gap-fill reaction was performed as described in Materials and Methods using the conditions for the Stoffel DNA polymerase. After completion of the gap-fill reaction with the formation of the circular DNA molecule by ligation, the desired DNA sequences were amplified using common primers flanking the 3' and 5' target sequences of the padlock probe (Fig. 1D). We measured the performance of the assay by running the amplified products on a 2%

agarose gel to determine the length of the amplified products. We concluded that the assay was successful and quite reproducible when the length of gap-fill sequences was 200 bases, but we found that the consistency and the reproducibility of the assay diminished as the size of the gap-fill region increased [supporting information (SI) Tables S1 and S2]."

Krishnakumar continues, "To test whether short padlock probes were limiting the gap-fill reaction, we needed to make longer probes. To this end, we developed a methodology for making probes that were 300 bases. We posited that the LPPs should (potentially) overcome the limitations of the smaller-size probes. In our current protocol, the ssDNA probe is produced from a specifically designed dsDNA template using a series of enzymatic reactions and selective removal of one of the strands using lambda exonuclease digestion. We first built the ''core'' construct of the template that is common to all probes. The core is composed of a common nucleic acid sequence, the spacer, derived from the bacteriophage lambda flanked by the amplification primers (Fig. 1A)."(page 9297, last paragraph).

While Krishnakumar teaches padlock probes (MIPs) to detect different size target sequences, Krishnakumar does not specifically teach the use of MIPs in which one MIP provides additional flanking sequences of the target region.

However, Blasczyk teaches, "Even if sequencing is performed in both directions, the ends of the templates will not yield readable sequencing ladders. Indeed, these problems can be solved by the use of 5' and 3' nested sequencing primers." (page 102 last paragraph-top of page 103).

Kotsch teaches, "The use of nested sequencing primers additionally increased the specificity and quality of the sequencing reactions." (495, 2ND column, bottom)

Nilsson teaches MIP, padlock probes and selector probes all are circularized by hybridization to target nucleic acids to target nucleic acids (Figure 1 and figure 2, throughout). Nilsson teaches the padlock probes use ligation, while MIPs and selector probes use gap filing and ligation (83, bottom 2nd column-85). Nilsson teaches the probes which are ligated are separated from non-closed probes by digestion (isolation). Nilsson in figure 3 demonstrates amplification of circularized probes. Nilsson teaches, "Currently, 12 000 MIPs can be amplified and analyzed in parallel. We expect that a similar, or greater, number of selector probes can be applied to amplify large sets of genomic DNA fragments for subsequent analysis using high-throughput sequencing technologies [24,25]. Much effort is being invested into developing low-cost sequencing methods with the ultimate goal of sequencing an entire human genome for $1000 [5]. A more realistic goal, in the shorter term, is to sequence only the interesting parts of the genome, for example, all exons: the selector technology could be combined profitably with several of the sequencing techniques to achieve this." (bottom 1st column page 87, top of 2nd column).

Nilsson concludes, "Detailed understanding of multicellular organisms and many human diseases will ultimately require analyses of individual cells in their natural tissue environment."(page 87, 2nd column 1st full paragraph).

Thus Nilsson suggest examination of human nucleic acids samples by use of circular probes including padlock, MIP and selector probes which are circularized by

hybridization, isolation, amplifying and sequencing to characterize disease states by the genetic status.

Nilsson does not specifically teach the use of overlapping probes or targeting overlapping sequences

Hardenbohl (Genome Research (2005) volume 15, pages 269-275) teaches, " Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

Chee et al (WO 95/11995) teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays to determine nucleic acid sequences (see Figure7 and page 37 line 10- page 38 line 34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and a target sequence for the identification of single base mutants possible in the reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases

(see page 18, lines 1-8). Chee teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-6). Chee teaches the probes are immobilized on an array. Chee teaches, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences' (page 32).

Johnson teaches, "The first genomic-scale study of transcription using microarrays was performed in Escherichia coli using probes 'tiled' at regular intervals (Box 1) to provide an unbiased view of transcription with respect to the locations of known and predicted genes [12"

Dong teaches methods and kits for amplification of target nucleic acids(abstract). Dong teaches the method before or in conjunction with sequencing (0115). Dong teaches some embodiments include amplification with ligase mediated amplification techniques including padlock probes (0109). Dong in 0087 teaches, "In some embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both."

Mockler teaches the use of tiling arrays to examine the whole genome including overlapping and nonoverlaping (figure 1).

Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165)

Streit teaches the CFTR gene has multiple mutations in close proximity in exon 11 (table 2) (s549Nm G542X, G551D and R553X).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use overlapping circularized probes such as MIPs, LPPs, padlock or selector probes using overlapping probes each have different nucleic acid arm sequences and thus capture additional flanking sequences and sequencing the MIP. The artisan would be motivated to use to detect specific mutations as the art teaches MIPs that are overlapping and demonstrates the use of MIP to detect previously unknown transcripts.. The artisan would have a reasonable expectation of success as the artisan is merely designing and circularized probes such as MIPs, padlock or selector probes to detect known mutations by known means.

With regards to claim 3-4, It would have been prima facie obvious to one of skill in the art prior at the time the invention was made that design padlock probes to detect fragments of 500 nucleotides the 3' and 5' targeting arms would not overlap have different sequences than padlock probes for detection of 200 nucleotides. The artisan would be motivated to provide targeting arms that are long enough to target the 200 or 500 nucleotide sequence without the expense of making them extremely long.

With regards to claim 68-69, Krishnakumar teaches MIPS with 2580-500 nucleotides in target region (figure 2).

With regards to claim 70, Krishnakumar teaches the use of 50 attomoles of the probes. Thus Krishnakumar teaches at least 2 different MIPS

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims.

5. Claims 72-73 rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Hardenbohl (Genome Research (2005) volume 15, pages 269-275) Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102)Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)) as applied to claim 1, 3-4, 68-71 above, and further in view of Chaisson (Bioinformatics (2004) volume 20, pages 2067-2074)

The teachings of Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee et al, Johnson, Blasczyk, Kotsch are set forth above.

While Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee et al, Johnson, Blasczyk, Kotsch teach sequencing of padlock probes (MIPs), they

do not specifically teach next generation sequencing or averaging sequence reads from at least 3 MIPS.

However, Chaisson teaches fragment assembly for short reads including 454 Life Sciences sequencer ((2067, 2nd column, 1st paragraph).. Chaisson teaches the next generation sequencing allow for greater coverage at a lower cost than Sanger sequencing. Chaisson teaches different methods of different read lengths (2067, 2nd column, 1st paragraph). Chaisson teaches determining average read length (page 2069, 2nd column bottom).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the arms of the MIPS and determine average read length. The artisan would be motivated to increasing the speed and coverage of sequencing while reducing the cost. The artisan would have a reasonable expectation of success as the artisan is using known methods of detecting sequences and determining average read length.

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims.

Summary

No claims are allowed.

Conclusion

1. 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 Monday- Friday about 6:00 AM-5:30 PM, 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.

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/Steven Pohnert/
Primary Examiner, Art Unit 1634

Notice of References Cited	Application/Control No. 13/266,862	Applicant(s)/Patent Under Reexamination Porreca et al.	
	Examiner STEVEN C POHNERT PhD	Art Unit 1634	Page 1 of 2

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20070212704-A1	09-2007	Dong; Shoulian	C12Q1/6848	435/6.12
	B					
	C					
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	U	Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88)
	V	Streit (Molecular Genetics and Metabolism (2003) volume 259-264)
	W	Mockler (Genomics (2005) volume 85, pages 1-15)
	X	Jares (Clin Trnal Oncology (2006) volume 8, pages 161-172)

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Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Petitioner Illumina, Inc., EX1002, p. 1975

Notice of References Cited	Application/Control No. 13/266,862	Applicant(s)/Patent Under Reexamination Porreca et al.	
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Petitioner Illumina, Inc., EX1002, p. 1976

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13266862
	Filing Date	2012-03-13
	First Named Inventor	Gregory Porreca
	Art Unit	1634
	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

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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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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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Art Unit	1634
Examiner Name	S. C. Pohnert
Attorney Docket Number	MLB-002/01US 34468/8

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	Examiner Name	S. C. Pohnert
	Attorney Docket Number	MLB-002/01US 34468/8

[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.

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /SP/

Electronic Acknowledgement Receipt	
EFS ID:	46835463
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Zachary D. Hyde/Matthew York
Filer Authorized By:	Zachary D. Hyde
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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-002-01US-Response-101722.pdf	138759 8d06f805bc8656bbe50c6a7cda19823e6bfd1d9e	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Request for Reconsideration-After Non-Final Rejection	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	11
Warnings:			
Information:			
	Total Files Size (in bytes):	138759	

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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.

Attorney Docket No. MLB-002/01US 34468/8

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosolutions, LLC	ART UNIT:	1634
APPL. NUMBER:	13/266,862	CONFIRMATION NO.:	6082
FILING DATE:	March 13, 2012	EXAMINER:	Pohnert, Steven C.
TITLE:	**METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS**		

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

FILED ELECTRONICALLY

RESPONSE

This paper is in response to the non-final Office Action mailed July 15, 2022, from the United States Patent and Trademark Office.

A **Listing of the Claims** begins on page 2.

Remarks begin on page 4.

Applicant submits that no fees are due with this response. Nevertheless, Applicant authorizes the Commissioner to charge any other required fee to Deposit Account No. 50-0369.

Listing of the Claims

1. (Previously presented) A method for analyzing a target nucleic acid, the method comprising:

providing a sample comprising nucleic acid comprising a target region;

contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes (MIPs) comprising different nucleotide sequences, each MIP comprising a 5' targeting arm, a central region, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region ;

converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target and some comprising the additional flanking nucleic acids;

isolating the plurality of circularized probes; and

analyzing the target region.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

4. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, different than the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

5-67. (Canceled)

Petitioner Illumina, Inc., EX1002, p. 1988

68. (Previously Presented) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized on either side of the target region, are separated by a plurality of nucleotides on the nucleic acid.

69. (Previously Presented) The method of claim 1, wherein the target region comprises at least 50 base pairs of DNA.

70. (Previously Presented) The method of claim 1, wherein each target region is captured by at least three different MIPs.

71. (Previously Presented) The method of claim 70, wherein the step of analyzing the target region comprises sequencing the copy of the target and the additional flanking nucleic acids to generate sequence reads.

72. (Previously Presented) The method of claim 71, wherein the sequencing is next generation sequencing.

73. (Previously presented) The method of claim 72, wherein the step of analyzing comprises averaging the nucleotide base-composition off the sequence reads from the at least three different MIPs.

Petitioner Illumina, Inc., EX1002, p. 1989

Remarks

Claims 1, 3, 4, and 68-69 are pending in the application, with claim 1 being the only independent claim. No amendments are made. No new matter is added.

Rejections under 35 U.S.C. §103(a)

The Office Action, at page 3, states that claims 1, 68, and 70-71 are rejected under 35 U.S.C. §103(a) over **Daly** (Clinical Chemistry, 2007, 53:1222-30) in view of **Hardenbohl** (Genome Research, 2005, 14:269-275), **Nilsson** (Trends in Biotechnology (2006) volume 24, pages 83-88), US Publication No. 2007-0212704 to **Dong**, **Streit** (Mol Genet and Metab (2003) 78(4):259-264), **Mockler** (Genomics (2005) 85(1), 1-15), **Jares** (Clin Trial Oncology (2006) volume 8, pages 161-172), PCT Publication No. WO 95/11995 to **Chee**, and **Johnson** (Trends in Genetics (2005) volume 21, pages 93-102).

The Office Action, at page 12, states that claims 1, 3-4, and 68-71 are rejected under 35 U.S.C. §103(a) over **Krishnakumar** (Proceedings National Academy of Sciences, 2008, 105: 9296-9301), Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, Johnson, **Blasczyk** (Tissue Antigens, 1996, 47:102-10), and **Kotsch** (Tissue Antigens, 1999, 52:486-97).

The Office Action, at page 20, states that claims 72-73 are rejected under 35 U.S.C. §103(a) over Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, Johnson, Blasczyk, Kotch, and **Chaisson** (Bioinformatics (2004) 30:2067-74).

The pending claims are not obvious over any combination of Daly, Hardenbohl, Nilsson Dong, Streit, Mockler, Jares, Chee, Johnson, Krishnakumar, Blasczyek, Kotch, or Chaisson.

In general, the Patent Office must establish three basic criteria in order to establish a prima facie case of obviousness. There must be a suggestion to modify a reference or to combine references to lead one of ordinary skill in the art to the claimed invention; the cited references must convey a reasonable expectation of success in arriving at the claimed invention; and the suggestion to modify the references must be found in the prior art, not in the applicant's

disclosure. *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991). An obviousness rejection cannot be established in the first place unless each claim element is disclosed in the cited art. *In re Royka,* 490 F.2d 981 (CCPA 1974). A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 220 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 851 (1984). The Federal Circuit has made clear that "while 'common sense' can be invoked, even potentially to supply a limitation missing from the prior art, it must still be supported by evidence and a reasoned explanation . . . [T]his is particularly true where the missing limitation goes to the heart of an invention." *Arendi v. Apple*, 832 F.3d 1355, 1363 (Fed. Cir. 2016).

The pending claims recite sets of MIPs in which multiple different MIPs capture the same target region and also capture different sets of nucleic acids flanking the target.

None of the cited references report a set of MIPs in which multiple different MIPs capture a single target, much less also binding to flanking sequences. Given that this element is missing in the cited art, Applicant believes that it is improper to maintain a rejection under 35 USC 103.

Daly does not disclose sets of MIPs in which different MIPs capture the same target region. Daly reports a MIP assay in which a single MIP is used to capture each target. Daly explicitly says that "a single best probe design for each locus" was chosen with only "a single probe for each variant." *Id. at 1224 (emphasis added)*. No two MIPs are used to interrogate a single region.

Daly also reports that "[e]ach locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." *Id.* That is, each locus in Daly is assayed with three copies of the same MIP, each copy having an identical nucleic acid sequence. Daly simply does not report the use of different MIPs with differing nucleic acid sequences to capture the same target region.

Hardenbohl and Nilsson

Neither Harenbohl nor Nilsson can remedy the deficiencies of Daly because both of those references suffer from the same deficiencies as Daly.

Like Daly, Hardenbohl reports the use of only a single MIP to capture each target region. Hardenbohl explicitly reports an assay which uses "only a single probe per SNP." *Hardenbohl, at page 272.* No two MIPs are used to interrogate a single region.

Hardenbohl also explicitly reports MIPs that do not capture any nucleic acids flanking a target. Hardenbohl reports that in its MIP assay, each MIP is "a single oligonucleotide probe with recognition sequences at each terminus is hybridized with a genomic target sequence such that it forms a circular structure, with the ends of the probe abutting. This leaves a single base gap at the location of a SNP." *Hardenbohl at 270 (emphasis added).* Because the probes interrogate only a single base of the target, they do not capture nucleic acids flanking the target.

Nilsson is also limited to the use of a single MIP to interrogate each target. Nilsson is a review article on SNP assays that use circularized probes, including MIPs. Nilsson specifically references Hardenbohl in reporting how MIP assays are designed. *Id. at 84.* That is, as Hardenbohl lays out, the MIP assay uses only a single probe per SNP. No two MIPs are used to interrogate a single region.

Like Hardenbohl, Nilsson also explicitly reports MIPs that do not capture any nucleic acids flanking a target. Nilsson reports that each "SNP is positioned between the ends of the padlock probe creating a single-nucleotide gap in the probe-target hetero-duplex." *Nilsson at 84, Figure 1(b) (emphasis added).* Like Hardenbohl, because the probes interrogate only a single base of a target nucleic acid, they do not capture nucleic acids flanking the target.

Dong, Streit, Mockler, Jares, Chee, Johnson

None of Dong, Streit, Mockler, Jares, Chee, Johnson can remedy the deficiencies of

Daly, Hardenbohl, and Nilsson, because none of Dong, Streit, Mockler, Jares, Chee, Johnson make any mention of MIPs at all and thus cannot reasonably be said to teach or suggest a set of MIPs in which different MIPs capture the same target sequence.

Dong reports the use of cleavage probe pairs that bind at sites upstream & downstream of a target in order to amplify a target. *Dong at [0060].* Dong reports that "these two sites are typically adjacent to each other." *Id.* When the pairs are adjacent, Dong reports that the adjacent pairs "may but need not overlap at least part of the downstream cleavage probe-binding site." *Id.* These are not MIPs. Moreover, multiple probes do not capture the same target.

Streit reports mutation detection in the CFTR gene. *Streit at Abstract and 261, Table 2.* Streit reports that the "[e]leven regions of the CFTR gene were amplified by PCR using specific oligonucleotide primers." *Id. at 260.* There are no MIPs in Streit and no two different primers that prime the same target. *Id. at 260, Table 1.*

Mockler is a review article on microarray tiling experiments. *Mockler at Abstract.* Mockler does not disclose the use of MIPS. The probes are each oligonucleotides designed against a known or predicted reference genome. The probes do not covalently-close to detect unknown bases between targeting arms. Rather, the sequence being detected needs to already be known. These probes are not MIPS. Moreover, only one probe, which matches to the target, binds to the target.

Jares, like Mockler, is also a review article comparing microarray tiling experiments of gene expression and DNA copy number. *Jares at Abstract.* The probes in Jares are not MIPS. Each probe is designed against a reference genome. For SNP detection, Jares uses two probes: one specific to the SNP, and one specific to wild-type. *Id., 167.* The probes do not detect unknown bases between targeting arms. These probes are not MIPS. Moreover, even still only one probe binds to the target depending on the base present.

Chee reports sets of 2-4 immobilized interrogation oligonucleotide probes, in which the probes differ at a single nucleotide position. *Chee at 2-3.* That single position is sampled against

each possible base call for that position. *Id.* That is to say, multiple probes interrogate a base pair, but only one probe, not two, can capture the base. Two different probes do not capture the same target. Moreover, there are no MIPs in Chee.

Johnson, like Mockler and Jares, reports microarray tiling experiments of gene expression. *Johnson, Abstract.* The probes discussed in Johnson are not MIPS. The probes are each oligonucleotides designed against a known or predicted reference genome. *Id. at 93.* The probes do not covalently-close to detect unknown bases between targeting arms. Rather, the sequence being detected needs to already be known. These probes are not MIPS.

Krishnakumar, Blasczyk, Kotsch, and Chaisson

None of Krishnakumar, Blasczyk, Kotsch, or Chaisson discloses sets of MIPs in which MIPs comprising different nucleic acid sequences capture the same target region.

Like Daly, Hardenbohl, and Nilsson, Krishnakumar also reports only the use of a single probe to capture each target. Two different probes do not capture the same target.

Specifically, Krishnakumar reports the use of long padlock probes (LPPs) "that are three times larger" than probes in a "conventional MIP assay." *Krishnakumar at 9297.* Krishnakumar reports the use of 557 LPPs to assay 485 exons. *Id.* Within the 485 exons, the probes assayed "575 target sequences representing human exons present in 30 kinase genes." *Id. at 9299.* Krishnakumar provides only 557 probes to assay 575 targets. This requires that each probe in Krishnakumar assay a different target. Krishnakumar does not and cannot teach the use of multiple probes having different sequences that capture the same target. Moreover, the probes in Krishnakumar and explicitly not MIPS.

Blasczyk makes no mention of MIPs or circularized probes at all. Blasczyk reports only the improvements to PCR products to overcome the limitations of Sanger sequencing. *Blasczyk, at page 102-103.* Blasczyk reports the use of two additional primers to capture the 5' and 3' ends of a target nucleic acid, typically lost during Sanger sequencing. The use of additional primers

taught in Blasczyk, however, is limited to specific Sanger sequencing techniques. Blasczyk clarifies that "the use of a nested approach requires the stocking of large amounts of sequencing primers. Hence, the application of dye primer sequencing techniques becomes infeasible." *Id. at 103.* This is an explicit teaching away from the use of nested primers in any technique other than Sanger sequencing. Even in mentioning a nested approach, no single primer even captures the entire target region, with a first primer capturing the majority of the target region and the 3' and 5' primers each capturing only 10-15 bases at the ends of the target region. *Id.*

Kotsch too makes no mention of MIPs or circularized probes. Kotsch makes no mention of multiple different MIPs capturing a single target nucleic acid. Like Blasczyk, Kotsch seeks to overcome drawbacks in PCR-SBT strategies that "that do not allow sequence analysis of the 5' and 3' ends of the 2nd exon" in HLA-DRB genes. *Kotsch at 487.* Kotch reports the use of three nested primers that correspond to three variants of a conserved region in the 3' end of intron 1 of the HLA-DRB gene. *Id. at 488.* Because the 3' end of intron 1 of the HLA-DRB gene has limited diversity, at least one of the three primers of Kotch is likely to hybridize with the 3' end of intron 1 in order to then amplify exon 2. *Id. at 496.* Kotsch teaches methods in which at most only a single primer is used to capture the target region. Multiple different primers do not capture a target region.

Chaisson also makes no mention of MIPS or any probes at all. Chaisson reports only that new computer-assisting assemblies may facilitate assembling short reads together, for example from pyrosequencing reads. *Chaisson at 2067-68.* Chaisson cannot remedy the deficiencies of Krishnakumar, Blasczyk, or Kotsch.

Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, and Johnson cannot remedy the deficiencies of Krishnakumar, Blasczyk, Kotsch, and Chaisson, because as discussed above with regard to Daly, none of these references teach a set of MIPs in which multiple MIPs capture a single target at all.

Petitioner Illumina, Inc., EX1002, p. 1995

Summary

The thirteen disparate references cited in this Official Action utterly fail to disclose the use of multiple different probes comprising different nucleic acid sequences for a single target region. The cited art represents the very prior art that the as-filed specification makes clear cannot achieve large uniformity or highly reproducible capture/amplification efficiency. *As-filed application at page 33, lines 16-20.* By using only single or multiple identical probes per target region, the cited art cannot average out error and bias, as provided by the claimed sets of MIPs with different sequences that capture a single region, as provided by the amended claims. *Id., at lines 27-29; see also New Claim 73.*

The lack of disclosure and failure to recognize the advantages of the claimed invention in the cited references emphasize that the claimed methods are non-obvious and should be allowed.

In view of the above remarks, Applicant believes that the rejections under section 103 are overcome.

Petitioner Illumina, Inc., EX1002, p. 1996

Conclusion

Applicant respectfully submits that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiner is invited and encouraged to contact Applicant's representative.

Dated: October 17, 2022

Respectfully submitted,
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Petitioner Illumina, Inc., EX1002, p. 1997

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8	6082

21710 7590 01/24/2023

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
01/24/2023	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.** 13/266,862	**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 10/17/2022.

☐ 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) 1,3-4 and 68-73 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) 1,3-4 and 68-73 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 4/8/2021 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., EX1002, p. 1999

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. 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 10/17/2022.

Claims 1, 3-4,68-73 are pending.

Claims 2, 5-67 have been canceled.

Claims 1, 3-4 and 68-73 are being examined.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Claim Rejections - 35 USC § 103

2. 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.

3. Claim 1, 68, 70-71 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Daly (Clinical Chemistry (2007)volume 53, pages 1222-1230),

Hardenbohl (Genome Research (2005) volume 15, pages 269-275), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102).

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of capture is not defined by the specification. Thus the broadest reasonable interpretation is allowing hybridization or isolation (consistent with page 7-8 of the specification).

The prior art of record exemplifies that MIP and their analysis was known. MIPs with overlapping sequences were known, as were methods of tiling. Thus the claims are nothing more than the predictable combination of known steps and elements as exemplified below.

Daly teaches, " Molecular inversion probe (MIP) technology is an oligonucleotide-based method that can be used to analyze several thousand SNPs in a single assay (20). This technique has been used extensively for the HapMap project (21) and offers several advantages for multiplex genotyping. First, PCR amplification occurs after mutation detection, at which time MIPs have been converted to standard-

length oligonucleotides of similar sequence composition utilizing common PCR primers. Second, the MIPs are designed to be locus-specific rather than allele specific and require only a single probe per marker, so any loss of performance of a probe will affect both alleles equally, avoiding unbalanced genotyping. Third, each probe has two recognition sequences as in PCR but retains unimolecular hybridization kinetics, enabling high multiplexing with low concentration requirements. Finally, the use of molecular tag sequences on the probes allows hybridization to the microarray to be independent of the gene sequence, increasing the specificity and sensitivity of detection and allowing for a high degree of flexibility in assay design (22)." (page 1223, 1st column top).

Daly continues, " We have applied MIP technology to develop an assay testing 1227 variants in 169 genes involved in drug metabolism. Within this set, we have chosen a core set of 165 variants in 27 genes for extensive analytical validation." (page 1223, 1st column, 2nd full paragraph).

Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

Daly does not teach the sequence of the probes or specifically teach probes with additional flanking region.

Nilsson teaches MIP, padlock probes and selector probes all are circularized by hybridization to target nucleic acids to target nucleic acids (Figure 1 and figure 2, throughout). Nilsson teaches the padlock probes use ligation, while MIPs and selector probes use gap filing and ligation (83, bottom 2nd column-85). Nilsson teaches the probes which are ligated are separated from non-closed probes by digestion (isolation). Nilsson in figure 3 demonstrates amplification of circularized probes. Nilsson teaches, "Currently, 12 000 MIPs can be amplified and analyzed in parallel. We expect that a similar, or greater, number of selector probes can be applied to amplify large sets of genomic DNA fragments for subsequent analysis using high-throughput sequencing technologies [24,25]. Much effort is being invested into developing low-cost sequencing methods with the ultimate goal of sequencing an entire human genome for $1000 [5]. A more realistic goal, in the shorter term, is to sequence only the interesting parts of the genome, for example, all exons: the selector technology could be combined profitably with several of the sequencing techniques to achieve this." (bottom 1st column page 87, top of 2nd column).

Nilsson concludes, "Detailed understanding of multicellular organisms and many human diseases will ultimately require analyses of individual cells in their natural tissue environment."(page 87, 2nd column 1st full paragraph).

Thus Nilsson suggest examination of human nucleic acids samples by use of circular probes including padlock, MIP and selector probes which are circularized by hybridization, isolation, amplifying and sequencing to characterize disease states by the genetic status.

Nilsson does not specifically teach the use of overlapping probes or targeting overlapping sequences

Hardenbohl (Genome Research (2005) volume 15, pages 269-275) teaches, " Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

Chee et al (WO 95/11995) teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays to determine nucleic acid sequences (see Figure7 and page 37 line 10- page 38 line 34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and a target sequence for the identification of single base mutants possible in the reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (see page 18, lines 1-8). Chee teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-

6). Chee teaches the probes are immobilized on an array. Chee teaches, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences' (page 32).

Johnson teaches, "The first genomic-scale study of transcription using microarrays was performed in Escherichia coli using probes 'tiled' at regular intervals (Box 1) to provide an unbiased view of transcription with respect to the locations of known and predicted genes [12"

Dong teaches methods and kits for amplification of target nucleic acids(abstract). Dong teaches the method before or in conjunction with sequencing (0115). Dong teaches some embodiments include amplification with ligase mediated amplification techniques including padlock probes (0109). Dong in 0087 teaches, "In some embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both."

Mockler teaches the use of tiling arrays to examine the whole genome including overlapping and nonoverlaping (figure 1).

Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165)

Streit teaches the CFTR gene has multiple mutations in close proximity in exon 11 (table 2) (s549Nm G542X, G551D and R553X).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use overlapping circularized probes such as MIPs, padlock or selector probes using overlapping probes each have different nucleic acid arm sequences and thus capture additional flanking sequences. The artisan would be motivated to use to detect specific mutations as the art teaches MIPs that are overlapping and demonstrates the use of MIP to detect previously unknown transcripts.. The artisan would have a reasonable expectation of success as the artisan is merely designing and circularized probes such as MIPs, padlock or selector probes to detect known mutations by known means.

Daly does not specifically converting to a closed circularized probe , isolating and analyzing.

However, Daly in the first cited paragraph references Hardenbohl (reference 20).

Hardenbohl teaches., "single oligonucleotide probe with recognition sequences at each terminus is hybridized with a genomic target sequence such that it forms a circular structure, with the ends of the probe abutting. This leaves a single base gap at the location of a SNP. This gapped-duplex is then tested in four separate reactions, each with a single dNTP species present, in which successful polymerization/ligation provides allelic differentiation. The probes are subsequently released from the genomic DNA and those that have been covalently circularized in the correct allele/nucleotide reaction combinations are amplified using a "universal" PCR primer pair. Each amplified probe contains a unique tag sequence that is complementary to a sequence on the universal tag array. Tags have been selected to have a similar Tm and base composition and to be maximally orthogonal in sequence complementarity. Amplicons are fluorescently

labeled and the tag sequences released from the genome homology regions using a restriction endonuclease treatment. The tags are then detected using a complementary tag array." (MIP technology, page 270).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to circularize, isolate and analyze the MIP and target region. The artisan would be motivated as Daly specifically references Hardenbohl. The artisan would have a reasonable expectation of success as the artisan is using art accepted probes in an art accepted manner.

With regards to claim 68, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that the detection of an insertion by a probe designed to detect a SNP would have a separation of a plurality of nucleotides (the insertion in addition to the SNP). The artisan would be motivated as Daly suggest the detection of insertions. The artisan would have a reasonable expectation of success as the artisan is using known probes by known methods.

With regards to claim 70, Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

With regards to claim 71, Hardenbohl teaches sequencing (674, 2nd column-675). Daly teaches sequencing (figure 1A).

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims. Further the response asserts, "None of the cited references report a set of MIPs in which multiple different MIPs capture a single target." This argument has been thoroughly reviewed but is not considered persuasive as all the teaches MIPs at a concentration and thus teach MIPs that multiple different MIPS capture a single target sequence.

The response continues by asserting the Day teaches away from multiple probes as the response asserts Daly teaches the use of a single probe for each locus. This argument has been thoroughly reviewed but is not considered persuasive as Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different. Further, Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T. Further, the art as a whole demonstrates the use of tiling arrays to capture regions or targets of interest. Thus using MIPs that tile across a target of interest renders this limitation obvious. The response continues by contradicting the previous argument the prior art does not teach multiple probes to a single locus by

conceding, "each locus in Daly is assayed with three copies of the same MIP, each copy having an identical nucleic acid sequence. Daly simply does not report the use of different MIPs with differing nucleic acid sequences to capture the same target region." This last argument is not persuasive as Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

The response continues by asserting that Hardenbohl does not correct the deficiencies. This argument is not persuasive for the reasons of record. The response continues by asserting, "Hardenbohl reports the use of only a single MIP to capture each target region. Hardenbohl explicitly reports an assay which uses "only a single probe per SNP." This argument has been thoroughly reviewed but is not considered persuasive as Hardenbohl also teaches," Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

The response continues by asserting Nilsson is limited to the use of a single MIP for the to interrogate each target. This argument has been thoroughly reviewed but it not considered persuasive as Nilsson teaches the use of selector probes for amplification of different target loci, which would encompass those loci. Thus selector probe allows for different target fragments which would include SNPs or deletion (as taught by Dahl) and thus different additional flanking nucleotides.

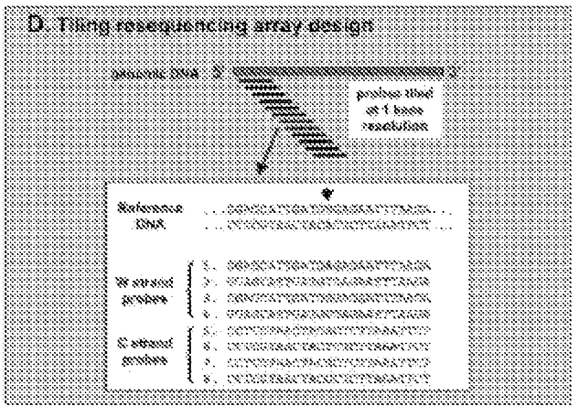
The response continues by asserting Dong, Streit, Mockler, Jares, Chee, Johnson do not cure the deficiencies. The response continues by asserting Dong, Streit, Mockler, Jares, Chee, Johnson do not specially teach or suggests MIP which capture additional flanking sequences to a target sequence. This argument has been

thoroughly reviewed but is not considered persuasive as Dong, Streit, Mockler, Jares, Chee, Johnson are not anticipatory references, but demonstrate designing probes with additional flanking sequences was known, rendering obvious the limitations of the probe as they are interpreted with respect to probe design.

The response continues by arguing Dong asserting, " Dong at [0060]. Dong reports that "these two sites are typically adjacent to each other." Id. When the pairs are adjacent, Dong reports that the adjacent pairs "may but need not overlap at least part of the downstream cleavage probe-binding site." This argument is not persuasive as the cited portion of Dong is an embodiment which is not being relied upon. Further , Dong teaches, "Dong in 0087 teaches, "In some embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both." Thus the response is picking and choosing parts of the prior art to try to confuse the teachings relied upon and thus the rejection at hand.

The response continues by conceding that Streit teaches the amplification and detection of mutations in CFTR, but does not teach. This argument has been thoroughly reviewed but is not considered persuasive as designing MIPS to target SNPs or areas around SNPs would result in MIPs that have additional flanking sequences including the recited SNPs.

The response concedes Mockler teaches a review microarray tiling strategies, but does not teach MIPs. The response continues to confuse the issue by limiting the discussion to SNPs. However, Mockler teaches



The response provides no evidence of unpredictability of use of tiling strategies reviewed by Mockler for the design of MIPs, the rejection relies upon.

The response concedes Jares teaches another review article on tiling arrays, but does not teach MIPS. This argument has been thoroughly reviewed but is not considered persuasive as Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165) The response provides no arguments to the use of tiling strategies in the design of MIPs which allow for inclusion of additional flanking sequences.

The response continues by conceding Chee also teaches methods of designing tiling probes which allow for the inclusion of additional flanking sequences in probe design, but asserts the teachings are limited to multiple probes to interrogate a different base. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not exclude multiple different MIPS to examine a single base. Further the tiling allows for additional flanking sequences in addition to the single base.

The response concedes Johnson teaches a probes of a microarray tiled across sequences of interest to detect gene expression of known sequences. The response asserts the tiling probes of Johnson to not detect unknown bases. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not require the capture of unknown bases.

The response concludes arguments by asserting the art of Dong, Streit, Mockler, Jares, Chee, Johnson do not teach MIPs. There is no evidence of unpredictability or unexpected results of using known strategies of probe design in the design of MIPs . Thus the rejection is maintained.

4. Claim 1, 3-4, 68-71 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Hardenbohl (Genome Research (2005) volume 15, pages 269-275) Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102)Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be

understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable

interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of capture is not defined by the specification. Thus the broadest reasonable interpretation is allowing hybridization or isolation (consistent with page 7-8 of the specification).

The prior art of record exemplifies that MIP and their analysis was known. MIPs with overlapping sequences were known, as were methods of tiling. Thus the claims are nothing more than the predictable combination of known steps and elements as exemplified below.

Krishnakumar teaches, "As a proof of principle, we used SMART technology to simultaneously amplify 485 human exons ranging from 100 to 500 bp from human genomic DNA. In multiple repetitions, >90% of the targets were successfully amplified with a high degree of uniformity, with 70% of targets falling within a 10-fold range and all products falling within a 100-fold range of each other in abundance. We used long padlock probes (LPPs) >300 bases in length for the assay, and the increased length of these probes allowed for the capture of human sequences up to 500 bp in length, which is optimal for capturing most human exons. To engineer the LPPs, we developed a method that generates ssDNA molecules with precise ends, using an appropriately designed dsDNA template. The template has appropriate restriction sites engineered into it that can be digested to generate nucleotide overhangs that are suitable for lambda exonuclease digestion, producing a single stranded probe from dsDNA. The SMART technology is flexible and can be easily adapted to multiplex tens of thousands of target sequences in a single reaction.."

Krishnakumar teaches, " In a series of singleplex assays, padlock probes that were 120 bases in length were annealed to human DNA, and the gap-fill reaction was performed as described in Materials and Methods using the conditions for the Stoffel DNA polymerase. After completion of the gap-fill reaction with the formation of the circular DNA molecule by ligation, the desired DNA sequences were amplified using common primers flanking the 3' and 5' target sequences of the padlock probe (Fig. 1D). We measured the performance of the assay by running the amplified products on a 2% agarose gel to determine the length of the amplified products. We concluded that the assay was successful and quite reproducible when the length of gap-fill sequences was 200 bases, but we found that the consistency and the reproducibility of the assay diminished as the size of the gap-fill region increased [supporting information (SI) Tables S1 and S2]."

Krishnakumar continues, "To test whether short padlock probes were limiting the gap-fill reaction, we needed to make longer probes. To this end, we developed a methodology for making probes that were 300 bases. We posited that the LPPs should (potentially) overcome the limitations of the smaller-size probes. In our current protocol, the ssDNA probe is produced from a specifically designed dsDNA template using a series of enzymatic reactions and selective removal of one of the strands using lambda exonuclease digestion. We first built the "core" construct of the template that is common to all probes. The core is composed of a common nucleic acid sequence, the spacer, derived from the bacteriophage lambda flanked by the amplification primers (Fig. 1A)."(page 9297, last paragraph).

While Krishnakumar teaches padlock probes (MIPs) to detect different size target sequences, Krishnakumar does not specifically teach the use of MIPs in which one MIP provides additional flanking sequences of the target region.

However, Blasczyk teaches, "Even if sequencing is performed in both directions, the ends of the templates will not yield readable sequencing ladders. Indeed, these problems can be solved by the use of 5' and 3' nested sequencing primers." (page 102 last paragraph-top of page 103).

Kotsch teaches, "The use of nested sequencing primers additionally increased the specificity and quality of the sequencing reactions." (495, 2ND column, bottom)

Nilsson teaches MIP, padlock probes and selector probes all are circularized by hybridization to target nucleic acids to target nucleic acids (Figure 1 and figure 2, throughout). Nilsson teaches the padlock probes use ligation, while MIPs and selector probes use gap filing and ligation (83, bottom 2nd column-85). Nilsson teaches the probes which are ligated are separated from non-closed probes by digestion (isolation). Nilsson in figure 3 demonstrates amplification of circularized probes. Nilsson teaches, "Currently, 12 000 MIPs can be amplified and analyzed in parallel. We expect that a similar, or greater, number of selector probes can be applied to amplify large sets of genomic DNA fragments for subsequent analysis using high-throughput sequencing technologies [24,25]. Much effort is being invested into developing low-cost sequencing methods with the ultimate goal of sequencing an entire human genome for $1000 [5]. A more realistic goal, in the shorter term, is to sequence only the interesting parts of the genome, for example, all exons: the selector technology could be combined profitably

with several of the sequencing techniques to achieve this." (bottom 1st column page 87, top of 2nd column).

Nilsson concludes, "Detailed understanding of multicellular organisms and many human diseases will ultimately require analyses of individual cells in their natural tissue environment."(page 87, 2nd column 1st full paragraph).

Thus Nilsson suggest examination of human nucleic acids samples by use of circular probes including padlock, MIP and selector probes which are circularized by hybridization, isolation, amplifying and sequencing to characterize disease states by the genetic status.

Nilsson does not specifically teach the use of overlapping probes or targeting overlapping sequences

Hardenbohl (Genome Research (2005) volume 15, pages 269-275) teaches, " Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

Chee et al (WO 95/11995) teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays to determine nucleic acid sequences (see Figure7 and page 37 line 10- page 38 line

34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and a target sequence for the identification of single base mutants possible in the reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (see page 18, lines 1-8). Chee teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-6). Chee teaches the probes are immobilized on an array. Chee teaches, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences' (page 32).

Johnson teaches, "The first genomic-scale study of transcription using microarrays was performed in Escherichia coli using probes 'tiled' at regular intervals (Box 1) to provide an unbiased view of transcription with respect to the locations of known and predicted genes [12"

Dong teaches methods and kits for amplification of target nucleic acids(abstract). Dong teaches the method before or in conjunction with sequencing (0115). Dong teaches some embodiments include amplification with ligase mediated amplification techniques including padlock probes (0109). Dong in 0087 teaches, "In some embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both."

Mockler teaches the use of tiling arrays to examine the whole genome including overlapping and nonoverlaping (figure 1).

Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165)

Streit teaches the CFTR gene has multiple mutations in close proximity in exon 11 (table 2) (s549Nm G542X, G551D and R553X).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use overlapping circularized probes such as MIPs, LPPs, padlock or selector probes using overlapping probes each have different nucleic acid arm sequences and thus capture additional flanking sequences and sequencing the MIP. The artisan would be motivated to use to detect specific mutations as the art teaches MIPs that are overlapping and demonstrates the use of MIP to detect previously unknown transcripts.. The artisan would have a reasonable expectation of success as the artisan is merely designing and circularized probes such as MIPs, padlock or selector probes to detect known mutations by known means.

With regards to claim 3-4, It would have been prima facie obvious to one of skill in the art prior at the time the invention was made that design padlock probes to detect fragments of 500 nucleotides the 3' and 5' targeting arms would not overlap have different sequences than padlock probes for detection of 200 nucleotides. The artisan would be motivated to provide targeting arms that are long enough to target the 200 or 500 nucleotide sequence without the expense of making them extremely long.

With regards to claim 68-69, Krishnakumar teaches MIPS with 2580-500 nucleotides in target region (figure 2).

With regards to claim 70, Krishnakumar teaches the use of 50 attomoles of the probes. Thus Krishnakumar teaches at least 2 different MIPS

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims.

The response asserts, "This requires that each probe in Krishnakumar assay a different target. Krishnakumar does not and cannot teach the use of multiple probes having different sequences that capture the same target.." This argument has been thoroughly reviewed but is not considered persuasive as Krishnakumar is not an anticipatory reference. The other cited prior art renders the limitations with respect to targeting additional flanking sequences obvious.

The response continues by asserting Blasczyk does not mention MIPs. This argument has been thoroughly reviewed but is not considered persuasive as Blasczyk is not relied upon for the teachings of MIPs. But, "Even if sequencing is performed in both directions, the ends of the templates will not yield readable sequencing ladders. Indeed, these problems can be solved by the use of 5' and 3' nested sequencing primers." (page 102 last paragraph-top of page 103)" which provides motivation why

one of skill in the art would want to design MIPs with different sequences to include flanking sequences. The response further provides arguments with respect to Sanger sequencing. This argument is not persuasive as the independent claim does not require sequencing.

The response continues by noting that Kotsch is not anticipatory and thus does not teach MIPs. The response concedes that Kotsch like Blasczyk teaches the issues of ambiguity of sequencing the 5' and 3' ends of sequences. The response continues conceding that Kotch teaches the use of nested primers which provide primers with different sequences which allow for capture of additional flanking nucleic acid sequences. The response further asserts primers do not capture a sequence. This argument has been thoroughly reviewed but is not considered persuasive as the claims and specification provide no limiting definition of capture. Thus the hybridization to primers is similar to the hybridization to the ends of MIPs.

The response notes that Chaisson does not teach MIPs. This is conceded by te action as Chaisson is not an anticipatory reference.

The response provides the general assertion of Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee and Johnson do not a set of MIPs which capture a single target at all. This argument has been thoroughly reviewed but is not considered persuasive as all the MIP reference teach the use of multiple copies of MIPs to detecxt a single target sequence.

The response concludes by arguing the individual references do not specifically teach MIPs that target a target nucleic acid (which encompasses a SNP) and additional flanking sequences. This argument is not persuasive as the art demonstrates method

of tiling or using nested arms (nested primers) which bind to additional flanking are obvious. The response has provided no evidence of unexpected results. Thus the rejection is maintained.

5. Claims 72-73 rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Hardenbohl (Genome Research (2005) volume 15, pages 269-275) Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102)Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)) as applied to claim 1, 3-4, 68-71 above, and further in view of Chaisson (Bioinformatics (2004) volume 20, pages 2067-2074)

The teachings of Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee et al, Johnson, Blasczyk, Kotsch are set forth above.

While Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee et al, Johnson, Blasczyk, Kotsch teach sequencing of padlock probes (MIPs), they do not specifically teach next generation sequencing or averaging sequence reads from at least 3 MIPS.

However, Chaisson teaches fragment assembly for short reads including 454 Life Sciences sequencer ((2067, 2nd column, 1st paragraph).. Chaisson teaches the next generation sequencing allow for greater coverage at a lower cost than Sanger sequencing. Chaisson teaches different methods of different read lengths (2067, 2nd column, 1st paragraph). Chaisson teaches determining average read length (page 2069, 2nd column bottom).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the arms of the MIPS and determine average read length. The artisan would be motivated to increasing the speed and coverage of sequencing while reducing the cost. The artisan would have a reasonable expectation of success as the artisan is using known methods of detecting sequences and determining average read length.

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims.

Summary

No claims are allowed.

Conclusion

1. **THIS ACTION IS MADE FINAL.** 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.

2. 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 Monday- Friday about 6:00 AM-5:30 PM, 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 published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-

center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven Pohnert/
Primary Examiner, Art Unit 1634

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
13/266,862	**01/30/2023 01:59:32 PM ET**	**MLB-002/01US 34468/8**

Title of Invention

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	6082	FILED BY	Kristina Scandore
PATENT CENTER #	61512774	FILING DATE	03/13/2012
CUSTOMER #	21710	FIRST NAMED INVENTOR	Gregory Porreca
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	John Serio

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
11746464_1_aia0080_Molecular Loop Biosciences, Inc._SIGNED.PDF	2	Power of Attorney	238 KB
11829923_1_MLB-002_01US STATEMENT UNDER 37 CFR 3.73.PDF	3	Assignee showing of ownership per 37 CFR 3.73	118 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)

11746464_1_aia0080_Molecular Loop Biosciences, Inc._SIGNED.PDF	770967D78E0EC32E67247DB39C9F3CF64A3AFF199B53CC8C8AC8799E42FA03A50F808EF7170209269902CADFB603671C8A406FD5BF39E82CC90009097CFA4B05
11829923_1_MLB-002_01US STATEMENT UNDER 37 CFR 3.73.PDF	0FC164CF3E33F27E479391A0FD146BC432A323932FF4F8915019BFC78717F54BDB47A5A064A4821B38D6AC77BB9C9B325E4FD58A949DD17B4ACF5493BBC008E1

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 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 03/31/2021. 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:

[X] Practitioners associated with Customer Number: 179511

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: 179511

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Molecular Loop Biosciences, Inc.
300 Tradecenter, Suite 5400, Woburn, MA 01801

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	Date 09-Jan-2023
Name Gregory Porreca	Telephone 978-254-7799
Title President 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)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: MOLECULAR LOOP BIOSCIENCES, INC.

Application No./Patent No.: 13/266,862 Filed/Issue Date: 03/13/2012

Titled: METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

MOLECULAR LOOP BIOSCIENCES, INC., 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. ☑ 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. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: GOOD START GENETICS, INC.

   The document was recorded in the United States Patent and Trademark Office at

   Reel 027860, Frame 0025, or for which a copy thereof is attached.

2. 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.

This collection of information is required by 37 CFR 3.73(b). 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. 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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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: MOLECULAR LOOP BIOSOLUTIONS, LLC To: MOLECULAR LOOP BIOSCIENCES, INC.

The document was recorded in the United States Patent and Trademark Office at
Reel 058263, Frame 0673, 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.

/John C. Serio/	January 30,2023
Signature	Date
John C. Serio	39023
Printed or Typed Name	Title or Registration Number

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.

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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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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 Acknowledgement Receipt	
EFS ID:	47887032
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas Meyers/Sandra Richards
Filer Authorized By:	Thomas Meyers
Attorney Docket Number:	MLB-002/01US 34468/8
Receipt Date:	24-APR-2023
Filing Date:	13-MAR-2012
Time Stamp:	12:28:54
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$800
RAM confirmation Number	E20234NC30035028
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	Request for Continued Examination (RCE)	MLB-002-01US-SRCE.pdf	1667156 37a457babdea1b9c6d55bb1c7912ab1a8c585ca7	no	3
Warnings:					
Information:					
2		MLB-002-01US-Response-042423.pdf	112791 f3304bc9ad3b2b30c617cfa2bfd203f8d3902925	yes	6
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	6	
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	37925 6c277ca49573f6adcb3cbd908639c657bcebde39	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1817872		

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New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (01-22)
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	13266862	Filing Date	2012-03-13	Docket Number (if applicable)	MLB-002-01US 1006120/9	Art Unit	1634
First Named Inventor	Gregory Porreca			Examiner Name	S. 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 604011

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 (01-22)
Approved for use through 05/31/2024. 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)	2023-04-24
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.

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosciences, Inc.		
APPLICATION NO.:	13/266,862	ART UNIT:	1634
FILING DATE:	March 13, 2012	CONF. NO.:	6082
EXAMINER:	S Pohnert		
TITLE:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS		

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

FILED ELECTRONICALLY

RESPONSE AND REQUEST FOR CONTINUED EXAMINATION (RCE)

This paper is in response to the final Office Action mailed January 24, 2023, from the United States Patent and Trademark Office.

Amendments to the claims begin on page 2.

Remarks begin on page 4.

A Request for Continued Examination (RCE) is submitted herewith. Applicant submits the fee for the RCE and authorizes any required fee to be charged to Deposit Account No. 604011.

12293892/1

Amendments to the claims:

Please amend the claims as follows.

1. (Previously presented) A method for analyzing a target nucleic acid, the method comprising:

providing a sample comprising nucleic acid comprising a target region;

contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes (MIPs) comprising different nucleotide sequences, each MIP comprising a 5' targeting arm, a central region, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region;

converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target and some comprising the additional flanking nucleic acids;

isolating the plurality of circularized probes; and

analyzing the target region.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

4. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, different than the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

5-67. (Canceled)

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68. (Previously Presented) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized on either side of the target region, are separated by a plurality of nucleotides on the nucleic acid.

69. (Previously Presented) The method of claim 1, wherein the target region comprises at least 50 base pairs of DNA

70. (Previously Presented) The method of claim 1, wherein each target region is captured by at least three different MIPs.

71. (Previously Presented) The method of claim 70, wherein the step of analyzing the target region comprises sequencing the copy of the target and the additional flanking nucleic acids to generate sequence reads.

72. (Previously Presented) The method of claim 71, wherein the sequencing is next generation sequencing.

73. (Previously presented) The method of claim 72, wherein the step of analyzing comprises averaging the nucleotide base-composition off the sequence reads from the at least three different MIPs.

74. (New) The method of claim 1, wherein the plurality of MIPs include at least a first MIP that includes a primer-binding region that can be used to sequence the target region.

75. (New) The method of claim 1, wherein each of the plurality of MIPs include a unique differentiator tag sequence.

76. (New) The method of claim 75, wherein the contacting step 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 about 0.05.

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Remarks

With entry of this amendment, claims 1, 3, 4, and 68-76 are pending, with claim 1 being the only independent claim. Claims 74-76 are new. Support for the amendments may be found throughout the as-filed application including, for example, (with reference to the version filed as PCT/US2010/001293) at least at line 27 on page 9 through line 6 on page 10 and lines 15-21 on page 9. No new matter is added.

Rejections under 35 U.S.C. §103

The Office Action on page 2 states that claims 1, 68, and 70-71 are rejected under §103 over Daly, 2007, Clin Chem 53(7):1222-1230, Hardenbohl, 2005, Gen Res 15:269-275, Nilsson, 2006, Trends Biotech 24(2):83-88, US 20070212704 to Dong, Streit, 2003, Mol Genet Metab 78(4):259-264, Mockler, 2005, Genomics 85:1-15, Jares, 2006, Clin Trans Oncol 8(3):161-172, WO 95/11995 to Chee, and Johnson, 2005, Trends Gen 21:93-102. On page 15, claims 1, 3-4, and 68-71 are so rejected over Krishnakumar, 2008, PNAS 105:9296-9301, Nilsson, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, Johnson, Blasczyk, 1996, Tiss Antigens 47:102-110), and Kotsch, 1999, Tiss Antigens 53:486-497. On page 25, claims 73-73 are so rejected over Krishnakumar, Nilsson, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, Johnson, Blasczyk, Kotsch, and Chaisson, 2004, Bioinformatics 20:2067-2074.

The claims are not obvious.

A determination of obviousness requires basic factual inquiries into the scope and content of the prior art as well as the differences between the claimed invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). A claim is only obvious where the skilled artisan would have been motivated to modify or combine references to arrive at the claimed invention with a reasonable expectation of success. *KSR v. Teleflex*, 550 U.S. 398, 418 (2007). When a patent claim includes a limitation that is wholly missing from the prior art, then that prior art does not support a conclusion of obviousness. *Arendi S.A.R.L. v. Apple, Inc.*, 832 F.3d 1355, 1366-67 (Fed. Cir. 2016).

Independent claim 1 recites a method for analyzing a target nucleic acid. As recited, the method includes contacting a target region in a nucleic acid with a plurality of MIPs. Claim

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states that each of the plurality of MIPs captures at least the target region. Further, some of the MIPs also capture additional sequence flanking the target.

That is, by the plain grammar and logic of claim 1 as written, a set of different MIPs all capture the same target. Some of those MIPs capture the target plus additional sequence.

The Office has still not found any single reference that uses a set of MIPs to redundantly capture one target with multiple different MIPs.

The only cited references that even mention MIPs are Daly, Hardenbohl, Nilsson, and Krishnakumar. The cited references to Dong, Streit, Mockler, Jares, Chee, Johnson, Blasczyk, Kotsch, and Chaisson do not mention MIPs whatsoever.

Against that background, for the Office to support a finding of obviousness, the Office must find among Daly, Hardenbohl, Nilsson, and Krishnakumar some teaching or suggestion of redundant or overlapping MIPs—multiple MIPs in one set that all capture the same target (with some of those capturing additional sequence by the target).

The Office has not done so.

Daly and Hardenbohl teach away from the claimed invention. Daly explicitly says that "a single best probe design for each locus" was chosen with only "a single probe for each variant." *Daly. 1224 (emphasis added)*. Hardenbohl requires an assay that uses "only a single probe per SNP." *Hardenbohl, 272*. Nilsson reports that each "SNP is positioned between the ends of the padlock probe creating a single-nucleotide gap in the probe-target hetero-duplex." *Nilsson at 84, Figure 1(b) (emphasis added, revealing that the Nilsson probes CANNOT capture additional sequence)*. Krishnakumar reports long padlock probes (LPPs), specifically using 557 probes to assay 575 targets, and in no case teaching multiple different probes being specific for the same target. *Krishnakumar, 9297, 9299*.

Because the Office has still not found any references that teach or suggest designing multiple MIPs against the same target, and because Office has still failed to show any motivation make such a probe set, the method of independent claim 1 is not obvious. Because the only independent claim is not obvious, none of the claims are obvious.

The rejections under §103 are unsupported and should be withdrawn.

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Conclusion

On the basis of the foregoing amendments and reasons, Applicant submits that the pending claims are in condition for allowance, which is respectfully requested.

Dated April 24, 2023

Respectfully submitted,
WITHERS BERGMAN LLP

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Petitioner Illumina, Inc., EX1002, p. 2045

Electronic Patent Application Fee Transmittal

Application Number:	13266862
Filing Date:	13-Mar-2012
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Filer:	Thomas Meyers/Sandra Richards
Attorney Docket Number:	MLB-002/01US 34468/8

Filed as Small Entity

Filing Fees for U.S. National Stage under 35 USC 371

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($)
Miscellaneous:				
RCE- 2ND AND SUBSEQUENT REQUEST	2820	1	800	800
		Total in USD ($)		**800**

Electronic Acknowledgement Receipt

EFS ID:	48078197
Application Number:	13266862
International Application Number:	
Confirmation Number:	6082
Title of Invention:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS
First Named Inventor/Applicant Name:	Gregory Porreca
Customer Number:	21710
Filer:	Thomas Meyers/Sandra Richards
Filer Authorized By:	Thomas Meyers
Attorney Docket Number:	MLB-002/01US 34468/8
Receipt Date:	31-MAY-2023
Filing Date:	13-MAR-2012
Time Stamp:	11:00:49
Application Type:	U.S. National Stage under 35 USC 371

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	Assignee showing of ownership per 37 CFR 3.73	MLB-002-01US-373c-statement.pdf	120656 b6a2c310c3871c0b68cf8b8dc8145858986 96cb6	no	3

Warnings:

Information:					
2	Power of Attorney	Molecular-Loop-POA-010923.pdf	168654 5ec7fee26f3770694f6de78b08c4e8ff766f2139	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	289310	

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/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Molecular Loop Biosciences, Inc.

Application No./Patent No.: 16/266862 Filed/Issue Date: March 13, 2012

Titled: METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Molecular Loop Biosciences, Inc., 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. ☑ 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. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Good Start Genetics, Inc.

   The document was recorded in the United States Patent and Trademark Office at

   Reel 027860, Frame 0025, or for which a copy thereof is attached.

2. 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.

This collection of information is required by 37 CFR 3.73(b). 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. 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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STATEMENT UNDER 37 CFR 3.73(c)

3. From: Molecular Loop Biosolutions, LLC To: Molecular Loop Biosciences, Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 058263, Frame 0673, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
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5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
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6. From: _____ To: _____

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/	May 31, 2023
Signature	Date
Thomas C. Meyers	36,989
Printed or Typed Name	Title or Registration Number

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.
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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.
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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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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: 179511

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: 179511

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Molecular Loop Biosciences, Inc.
300 Tradecenter, Suite 5400, Woburn, MA 01801

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	Date09-Jan-2023
NameGregory Porreca	Telephone978-254-7799
TitlePresident 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.**

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8

CONFIRMATION NO. 6082

179511
Withers Bergman LLP
101 Federal Street, Suite 1900
Boston, MA 02110

POA ACCEPTANCE LETTER

OC000000058012820

Date Mailed: 06/08/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/30/2023.

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**.

/sleutchit/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8

CONFIRMATION NO. 6082

21710
BROWN RUDNICK LLP
ONE FINANCIAL CENTER
BOSTON, MA 02111

POWER OF ATTORNEY NOTICE

OC000000058012756

Date Mailed: 06/08/2023

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/30/2023.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(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**.

/sleutchit/

Petitioner Illumina, Inc., EX1002, p. 2056

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 34468/8	6082

179511 7590 09/06/2023

Withers Bergman LLP
101 Federal Street, Suite 1900
Boston, MA 02110

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
09/06/2023	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):

Samantha.Metcalf@withersworldwide.com
US.Docketing@withersworldwide.com
kristina.scandore@withersworldwide.com

Office Action Summary	**Application No.** 13/266,862	**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 4/24/2023.

☐ 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) 1,3-4 and 68-76 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) 1,3-4 and 68-76 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 4/8/2021 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., EX1002, p. 2058

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. 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 4/24/2023 has been entered.

Claim Status and Formal matters

This action is in response to papers filed 4/24/2023.

Claims 1, 3-4,68-76 are pending.

Claims 74-76 have been added by amendment.

Claims 2, 5-67 have been canceled.

Claims 1, 3-4 and 68-76 are being examined.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Claim Rejections - 35 USC § 112

1. 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.

2. Claim 76 is 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 applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention.

The phrase "less than about 0.05" in claim 76 is indefinite. The MPEP states that relative terms such as "at least about" can present an issue of indefiniteness when there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range of specific activity is covered by the term "about". Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). See MPEP § 2173.05(b). In this case, the terms less than about 0.05" and "about" are not defined by the claim, the specification does not provide a sufficient standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus, the phrase “less than about 0.05" is undefined since an ordinary artisan would not have a proper basis from which to know what the limitation can be less than about 0.05. Thus, one of ordinary skill in the art could reasonably construe " less than about 0.05" to be a variety of subjective values. Since one of ordinary skill in the art could not be expected to make a reasonable distinction in the absence of further definitions and/or guidance in the

specification, the metes and bounds of claims 76, and all claims dependent thereon are indefinite.

Response to Arguments

This is a new ground of rejection necessitated by amendment.

Claim Rejections - 35 USC § 103

2. 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.

3. Claim 1, 68, 70-71, 75-76 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Daly (Clinical Chemistry (2007)volume 53, pages 1222-1230), Hardenbohl (Genome Research (2005) volume 15, pages 269-275), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metabolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102).

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be

understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable

interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of capture is not defined by the specification. Thus the broadest reasonable interpretation is allowing hybridization or isolation (consistent with page 7-8 of the specification).

The prior art of record exemplifies that MIP and their analysis was known. MIPs with overlapping sequences were known, as were methods of tiling. Thus the claims are nothing more than the predictable combination of known steps and elements as exemplified below.

Daly teaches, " Molecular inversion probe (MIP) technology is an oligonucleotide-based method that can be used to analyze several thousand SNPs in a single assay (20). This technique has been used extensively for the HapMap project (21) and offers several advantages for multiplex genotyping. First, PCR amplification occurs after mutation detection, at which time MIPs have been converted to standard-length oligonucleotides of similar sequence composition utilizing common PCR primers. Second, the MIPs are designed to be locus-specific rather than allele specific and require only a single probe per marker, so any loss of performance of a probe will affect both alleles equally, avoiding unbalanced genotyping. Third, each probe has two recognition sequences as in PCR but retains unimolecular hybridization kinetics, enabling high multiplexing with low concentration requirements. Finally, the use of molecular tag sequences on the probes allows hybridization to the microarray to be independent of the gene sequence, increasing the specificity and sensitivity of

detection and allowing for a high degree of flexibility in assay design (22)." (page 1223, 1st column top).

Daly continues, " We have applied MIP technology to develop an assay testing 1227 variants in 169 genes involved in drug metabolism. Within this set, we have chosen a core set of 165 variants in 27 genes for extensive analytical validation." (page 1223, 1st column, 2nd full paragraph).

Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

Daly does not teach the sequence of the probes or specifically teach probes with additional flanking region.

Nilsson teaches MIP, padlock probes and selector probes all are circularized by hybridization to target nucleic acids to target nucleic acids (Figure 1 and figure 2, throughout). Nilsson teaches the padlock probes use ligation, while MIPs and selector probes use gap filing and ligation (83, bottom 2nd column-85). Nilsson teaches the probes which are ligated are separated from non-closed probes by digestion (isolation). Nilsson in figure 3 demonstrates amplification of circularized probes. Nilsson teaches, "Currently, 12 000 MIPs can be amplified and analyzed in parallel. We expect that a similar, or greater, number of selector probes can be applied to amplify large sets of

genomic DNA fragments for subsequent analysis using high-throughput sequencing technologies [24,25]. Much effort is being invested into developing low-cost sequencing methods with the ultimate goal of sequencing an entire human genome for $1000 [5]. A more realistic goal, in the shorter term, is to sequence only the interesting parts of the genome, for example, all exons: the selector technology could be combined profitably with several of the sequencing techniques to achieve this." (bottom 1st column page 87, top of 2nd column).

Nilsson concludes, "Detailed understanding of multicellular organisms and many human diseases will ultimately require analyses of individual cells in their natural tissue environment."(page 87, 2nd column 1st full paragraph).

Thus Nilsson suggest examination of human nucleic acids samples by use of circular probes including padlock, MIP and selector probes which are circularized by hybridization, isolation, amplifying and sequencing to characterize disease states by the genetic status.

Nilsson does not specifically teach the use of overlapping probes or targeting overlapping sequences

Hardenbohl (Genome Research (2005) volume 15, pages 269-275) teaches, " Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

Chee et al (WO 95/11995) teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms

associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays to determine nucleic acid sequences (see Figure7 and page 37 line 10- page 38 line 34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and a target sequence for the identification of single base mutants possible in the reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (see page 18, lines 1-8). Chee teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-6). Chee teaches the probes are immobilized on an array. Chee teaches, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences' (page 32).

Johnson teaches, "The first genomic-scale study of transcription using microarrays was performed in Escherichia coli using probes 'tiled' at regular intervals (Box 1) to provide an unbiased view of transcription with respect to the locations of known and predicted genes [12"

Dong teaches methods and kits for amplification of target nucleic acids(abstract). Dong teaches the method before or in conjunction with sequencing (0115). Dong teaches some embodiments include amplification with ligase mediated amplification techniques including padlock probes (0109). Dong in 0087 teaches, "In some embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both."

Mockler teaches the use of tiling arrays to examine the whole genome including overlapping and nonoverlaping (figure 1).

Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165)

Streit teaches the CFTR gene has multiple mutations in close proximity in exon 11 (table 2) (s549Nm G542X, G551D and R553X).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use overlapping circularized probes such as MIPs, padlock or selector probes using overlapping probes each have different nucleic acid arm sequences and thus capture additional flanking sequences. The artisan would be motivated to use to detect specific mutations as the art teaches MIPs that are overlapping and demonstrates the use of MIP to detect previously unknown transcripts.. The artisan would have a reasonable expectation of success as the artisan is merely designing and circularized probes such as MIPs, padlock or selector probes to detect known mutations by known means.

Daly does not specifically converting to a closed circularized probe , isolating and analyzing.

However, Daly in the first cited paragraph references Hardenbohl (reference 20).

Hardenbohl teaches., "single oligonucleotide probe with recognition sequences at each terminus is hybridized with a genomic target sequence such that it forms a circular structure, with the ends of the probe abutting. This leaves a single base gap at the location of a SNP. This gapped-duplex is then tested in four separate reactions, each with a single dNTP species present, in which successful polymerization/ligation provides allelic differentiation. The probes are subsequently released from the genomic DNA and those that have been covalently circularized in the correct allele/nucleotide reaction combinations are amplified using a "universal" PCR primer pair. Each amplified probe contains a unique tag sequence that is complementary to a sequence on the universal tag array. Tags have been selected to have a similar Tm and base composition and to be maximally orthogonal in sequence complementarity. Amplicons are fluorescently labeled and the tag sequences released from the genome homology regions using a restriction endonuclease treatment. The tags are then detected using a complementary tag array." (MIP technology, page 270).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to circularize, isolate and analyze the MIP and target region. The artisan would be motivated as Daly specifically references Hardenbohl. The artisan would have a reasonable expectation of success as the artisan is using art accepted probes in an art accepted manner.

With regards to claim 68, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that the detection of an insertion by a probe designed to detect a SNP would have a separation of a plurality of nucleotides (the insertion in addition to the SNP). The artisan would be motivated as Daly suggest the detection of insertions. The artisan would have a reasonable expectation of success as the artisan is using known probes by known methods.

With regards to claim 70, Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

With regards to claim 71, Hardenbohl teaches sequencing (674, 2nd column-675). Daly teaches sequencing (figure 1A).

With regards to claim 75-76, Hardenbohl teaches., "Each amplified probe contains a unique tag sequence …." (MIP technology, page 270).

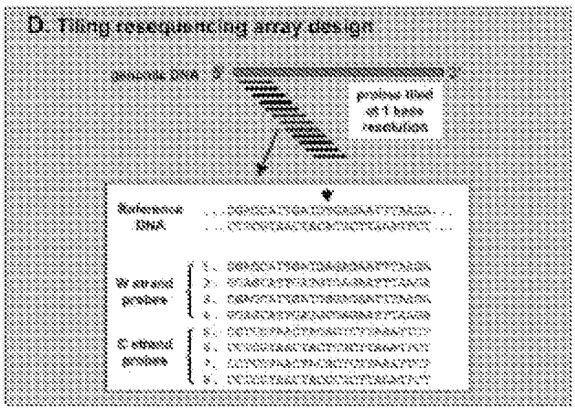
Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims. Further the response asserts, "None of the cited references

report a set of MIPs in which multiple different MIPs capture a single target." This argument has been thoroughly reviewed but is not considered persuasive as all the teaches MIPs at a concentration and thus teach MIPs that multiple different MIPS capture a single target sequence.

The response continues by asserting the Daly teaches away from multiple probes as the response asserts Daly teaches the use of a single probe for each locus. This argument has been thoroughly reviewed but is not considered persuasive as Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different. Further, Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T. Further, the art as a whole demonstrates the use of tiling arrays to capture regions or targets of interest. Thus using MIPs that tile across a target of interest renders this limitation obvious. The response continues by contradicting the previous argument the prior art does not teach multiple probes to a single locus by conceding, "each locus in Daly is assayed with three copies of the same MIP, each copy having an identical nucleic acid sequence. Daly simply does not report the use of different MIPs with differing nucleic acid sequences to capture the same target region." This last argument is not persuasive as Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

Mockler teaches a review microarray tiling strategies, but does not teach MIPs. The response continues to confuse the issue by limiting the discussion to SNPs. However, Mockler teaches



The response of 10/17/2022 concedes Jares teaches another review article on tiling arrays, but does not teach MIPS. This argument has been thoroughly reviewed but is not considered persuasive as Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165) The response provides no arguments to the use of tiling strategies in the design of MIPs which allow for inclusion of additional flanking sequences.

The response of 10/17/2022 continues by conceding Chee also teaches methods of designing tiling probes which allow for the inclusion of additional flanking sequences in probe design, but asserts the teachings are limited to multiple probes to interrogate a different base. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not exclude multiple different MIPS to examine a single

base. Further the tiling allows for additional flanking sequences in addition to the single base.

The response of 10/17/2022 concedes Johnson teaches a probes of a microarray tiled across sequences of interest to detect gene expression of known sequences. The response asserts the tiling probes of Johnson to not detect unknown bases. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not require the capture of unknown bases.

The response of 10/17/2022 concludes arguments by asserting the art of Dong, Streit, Mockler, Jares, Chee, Johnson do not teach MIPs. There is no evidence of unpredictability or unexpected results of using known strategies of probe design in the design of MIPs . Thus the rejection is maintained.

4. Claim 1, 3-4, 68-71, 74-76 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metabolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Hardenbohl (Genome Research (2005) volume 15, pages 269-275) Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102)Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)

MPEP 2111 states:

The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of capture is not defined by the specification. Thus the broadest reasonable interpretation is allowing hybridization or isolation (consistent with page 7-8 of the specification).

The prior art of record exemplifies that MIP and their analysis was known. MIPs with overlapping sequences were known, as were methods of tiling. Thus the claims are nothing more than the predictable combination of known steps and elements as exemplified below.

Krishnakumar teaches, "As a proof of principle, we used SMART technology to simultaneously amplify 485 human exons ranging from 100 to 500 bp from human genomic DNA. In multiple repetitions, >90% of the targets were successfully amplified with a high degree of uniformity, with 70% of targets falling within a 10-fold range and all products falling within a 100-fold range of each other in abundance. We used long padlock probes (LPPs) >300 bases in length for the assay, and the increased length of these probes allowed for the capture of human sequences up to 500 bp in length, which is optimal for capturing most human exons. To engineer the LPPs, we developed a method that generates ssDNA molecules with precise ends, using an appropriately designed dsDNA template. The template has appropriate restriction sites engineered into it that can be digested to generate nucleotide overhangs that are suitable for lambda exonuclease digestion, producing a single stranded probe from dsDNA. The

SMART technology is flexible and can be easily adapted to multiplex tens of thousands of target sequences in a single reaction.."

Krishnakumar teaches, " In a series of singleplex assays, padlock probes that were 120 bases in length were annealed to human DNA, and the gap-fill reaction was performed as described in Materials and Methods using the conditions for the Stoffel DNA polymerase. After completion of the gap-fill reaction with the formation of the circular DNA molecule by ligation, the desired DNA sequences were amplified using common primers flanking the 3' and 5' target sequences of the padlock probe (Fig. 1D). We measured the performance of the assay by running the amplified products on a 2% agarose gel to determine the length of the amplified products. We concluded that the assay was successful and quite reproducible when the length of gap-fill sequences was 200 bases, but we found that the consistency and the reproducibility of the assay diminished as the size of the gap-fill region increased [supporting information (SI) Tables S1 and S2]."

Krishnakumar continues, "To test whether short padlock probes were limiting the gap-fill reaction, we needed to make longer probes. To this end, we developed a methodology for making probes that were 300 bases. We posited that the LPPs should (potentially) overcome the limitations of the smaller-size probes. In our current protocol, the ssDNA probe is produced from a specifically designed dsDNA template using a series of enzymatic reactions and selective removal of one of the strands using lambda exonuclease digestion. We first built the "core" construct of the template that

is common to all probes. The core is composed of a common nucleic acid sequence, the spacer, derived from the bacteriophage lambda flanked by the amplification primers (Fig. 1A)."(page 9297, last paragraph).

While Krishnakumar teaches padlock probes (MIPs) to detect different size target sequences, Krishnakumar does not specifically teach the use of MIPs in which one MIP provides additional flanking sequences of the target region.

However, Blasczyk teaches, "Even if sequencing is performed in both directions, the ends of the templates will not yield readable sequencing ladders. Indeed, these problems can be solved by the use of 5' and 3' nested sequencing primers." (page 102 last paragraph-top of page 103).

Kotsch teaches, "The use of nested sequencing primers additionally increased the specificity and quality of the sequencing reactions." (495, 2ND column, bottom)

Nilsson teaches MIP, padlock probes and selector probes all are circularized by hybridization to target nucleic acids to target nucleic acids (Figure 1 and figure 2, throughout). Nilsson teaches the padlock probes use ligation, while MIPs and selector probes use gap filing and ligation (83, bottom 2nd column-85). Nilsson teaches the probes which are ligated are separated from non-closed probes by digestion (isolation). Nilsson in figure 3 demonstrates amplification of circularized probes. Nilsson teaches, "Currently, 12 000 MIPs can be amplified and analyzed in parallel. We expect that a similar, or greater, number of selector probes can be applied to amplify large sets of genomic DNA fragments for subsequent analysis using high-throughput sequencing technologies [24,25]. Much effort is being invested into developing low-cost sequencing methods with the ultimate goal of sequencing an entire human genome for $1000 [5]. A

more realistic goal, in the shorter term, is to sequence only the interesting parts of the genome, for example, all exons: the selector technology could be combined profitably with several of the sequencing techniques to achieve this." (bottom 1st column page 87, top of 2nd column).

Nilsson concludes, "Detailed understanding of multicellular organisms and many human diseases will ultimately require analyses of individual cells in their natural tissue environment."(page 87, 2nd column 1st full paragraph).

Thus Nilsson suggest examination of human nucleic acids samples by use of circular probes including padlock, MIP and selector probes which are circularized by hybridization, isolation, amplifying and sequencing to characterize disease states by the genetic status.

Nilsson does not specifically teach the use of overlapping probes or targeting overlapping sequences

Hardenbohl (Genome Research (2005) volume 15, pages 269-275) teaches, " Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

Chee et al (WO 95/11995) teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an

array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays to determine nucleic acid sequences (see Figure7 and page 37 line 10- page 38 line 34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and a target sequence for the identification of single base mutants possible in the reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (see page 18, lines 1-8). Chee teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-6). Chee teaches the probes are immobilized on an array. Chee teaches, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences' (page 32).

Johnson teaches, "The first genomic-scale study of transcription using microarrays was performed in Escherichia coli using probes 'tiled' at regular intervals (Box 1) to provide an unbiased view of transcription with respect to the locations of known and predicted genes [12"

Dong teaches methods and kits for amplification of target nucleic acids(abstract). Dong teaches the method before or in conjunction with sequencing (0115). Dong teaches some embodiments include amplification with ligase mediated amplification techniques including padlock probes (0109). Dong in 0087 teaches, "In some

embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both."

Mockler teaches the use of tiling arrays to examine the whole genome including overlapping and nonoverlaping (figure 1).

Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165)

Streit teaches the CFTR gene has multiple mutations in close proximity in exon 11 (table 2) (s549Nm G542X, G551D and R553X).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use overlapping circularized probes such as MIPs, LPPs, padlock or selector probes using overlapping probes each have different nucleic acid arm sequences and thus capture additional flanking sequences and sequencing the MIP. The artisan would be motivated to use to detect specific mutations as the art teaches MIPs that are overlapping and demonstrates the use of MIP to detect previously unknown transcripts.. The artisan would have a reasonable expectation of success as the artisan is merely designing and circularized probes such as MIPs, padlock or selector probes to detect known mutations by known means.

With regards to claim 3-4, It would have been prima facie obvious to one of skill in the art prior at the time the invention was made that design padlock probes to detect fragments of 500 nucleotides the 3' and 5' targeting arms would not overlap have different sequences than padlock probes for detection of 200 nucleotides. The artisan

would be motivated to provide targeting arms that are long enough to target the 200 or 500 nucleotide sequence without the expense of making them extremely long.

With regards to claim 68-69, Krishnakumar teaches MIPS with 2580-500 nucleotides in target region (figure 2).

With regards to claim 70, Krishnakumar teaches the use of 50 attomoles of the probes. Thus Krishnakumar teaches at least 2 different MIPS.

With regards to claim 74, Krishnakumar teaches, ", the desired DNA sequences were amplified using common primers flanking the 3' and 5' target sequences of the padlock probe (Fig. 1D)."

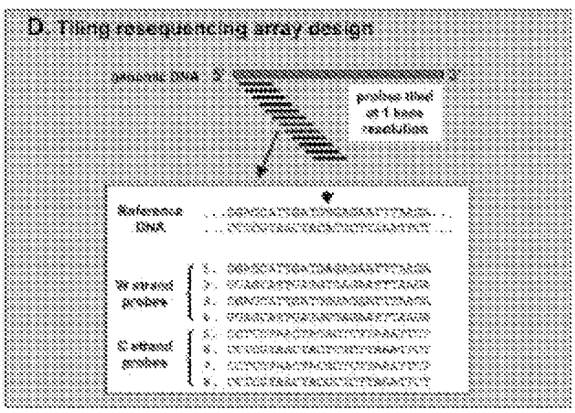
With regards to claim 75-76, Hardenbohl teaches., "Each amplified probe contains a unique tag sequence …." (MIP technology, page 270).

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims. Further the response asserts, "None of the cited references report a set of MIPs in which multiple different MIPs capture a single target." This argument has been thoroughly reviewed but is not considered persuasive as all the teaches MIPs at a concentration and thus teach MIPs that multiple different MIPS capture a single target sequence.

The response continues by asserting the Daly teaches away from multiple probes as the response asserts Daly teaches the use of a single probe for each locus. This argument has been thoroughly reviewed but is not considered persuasive as Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different. Further, Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T. Further, the art as a whole demonstrates the use of tiling arrays to capture regions or targets of interest. Thus using MIPs that tile across a target of interest renders this limitation obvious. The response continues by contradicting the previous argument the prior art does not teach multiple probes to a single locus by conceding, "each locus in Daly is assayed with three copies of the same MIP, each copy having an identical nucleic acid sequence. Daly simply does not report the use of different MIPs with differing nucleic acid sequences to capture the same target region." This last argument is not persuasive as Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

Mockler teaches a review microarray tiling strategies, but does not teach MIPs. The response continues to confuse the issue by limiting the discussion to SNPs. However, Mockler teaches



The response of 10/17/2022 concedes Jares teaches another review article on tiling arrays, but does not teach MIPS. This argument has been thoroughly reviewed but is not considered persuasive as Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165) The response provides no arguments to the use of tiling strategies in the design of MIPs which allow for inclusion of additional flanking sequences.

The response of 10/17/2022 continues by conceding Chee also teaches methods of designing tiling probes which allow for the inclusion of additional flanking sequences in probe design, but asserts the teachings are limited to multiple probes to interrogate a different base. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not exclude multiple different MIPS to examine a single base. Further the tiling allows for additional flanking sequences in addition to the single base.

The response of 10/17/2022 concedes Johnson teaches a probes of a microarray tiled across sequences of interest to detect gene expression of known

sequences. The response asserts the tiling probes of Johnson to not detect unknown bases. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not require the capture of unknown bases.

The response of 10/17/2022 concludes arguments by asserting the art of Dong, Streit, Mockler, Jares, Chee, Johnson do not teach MIPs. There is no evidence of unpredictability or unexpected results of using known strategies of probe design in the design of MIPs . Thus the rejection is maintained.

5. Claims 72-73 rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Hardenbohl (Genome Research (2005) volume 15, pages 269-275) Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102)Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)) as applied to claim 1, 3-4, 68-71 above, and further in view of Chaisson (Bioinformatics (2004) volume 20, pages 2067-2074)

The teachings of Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee et al, Johnson, Blasczyk, Kotsch are set forth above.

While Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee et al, Johnson, Blasczyk, Kotsch teach sequencing of padlock probes (MIPs), they

do not specifically teach next generation sequencing or averaging sequence reads from at least 3 MIPS.

However, Chaisson teaches fragment assembly for short reads including 454 Life Sciences sequencer ((2067, 2nd column, 1st paragraph).. Chaisson teaches the next generation sequencing allow for greater coverage at a lower cost than Sanger sequencing. Chaisson teaches different methods of different read lengths (2067, 2nd column, 1st paragraph). Chaisson teaches determining average read length (page 2069, 2nd column bottom).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the arms of the MIPS and determine average read length. The artisan would be motivated to increasing the speed and coverage of sequencing while reducing the cost. The artisan would have a reasonable expectation of success as the artisan is using known methods of detecting sequences and determining average read length.

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims.

Summary

No claims are allowed.

Conclusion

3. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bertone (.Chromosome Research 13: 259–274, 2005)

Fan (nature reviews genetics (2006) volume , pages 632-644).

4. 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 Monday- Friday about 6:00 AM-5:00 PM, 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, Winston Shen can be reached on 571-272-3157. 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. 13/266,862	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					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Bertone (.Chromosome Research 13: 259–274, 2005)
	V	Fan (nature reviews genetics (2006) volume , pages 632-644)
	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., EX1002, p. 2087

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
13/266,862	**12/06/2023 01:08:49 PM Z ET**	**MLB-002/01US 34468/8**

Title of Invention

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	6082	FILED BY	Sandra Richards
PATENT CENTER #	63507222	FILING DATE	03/13/2012
CUSTOMER #	179511	FIRST NAMED INVENTOR	Gregory Porreca
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Zachary Hyde

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
MLB-002-01US-Response-120623.pdf		8	-	119 KB
MLB-002-01US-Response-120623-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	70 KB
MLB-002-01US-Response-120623-CLM.pdf	(2-3)	2	Claims	52 KB
MLB-002-01US-Response-120623-REM.pdf	(4-8)	5	Applicant Arguments/Remarks Made in an Amendment	92 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
MLB-002-01US-Response-120623.pdf	A40E7962874C4722B4E509E5CE992954B21275693DD2D0E1B6F37DE4AE5B46A4E0D4E04C2C82EB5AFDEF19F7C410D06E61894B50E07CA240E02856041F84D192
MLB-002-01US-Response-120623-A...pdf	5B6149FB8BA8D70CD1073908344119D3515BFE5DA246C3AFE115A0F9204B95C72478AA9CFD2D30BD74EFA2475910D7142578D87E8C8836C2734074254D7DFB3A
MLB-002-01US-Response-120623-CLM.pdf	E8B501EF6C1E228B0211CC99FACA07D2E8097D06FEDFE0A1751E43624E390E9A63B4A224143B697E8FB15A9E2E93AB362D90BA3D04E118A63F6ADCC18725892A
MLB-002-01US-Response-120623-REM.pdf	9ACF1ECAB42C2229EB1AA04DE5CDF626B8975C6142FE65A46BC41D10BD2B1D6E725D9BA933C68C1C6C0F6C440E70005E1DE2810C6480802F759D2377D66A39F1

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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 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

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosciences, Inc.		
APPLICATION NO.:	13/266,862	ART UNIT:	1634
FILING DATE:	March 13, 2012	CONF. NO.:	6082
EXAMINER:	Steven Pohnert		
TITLE:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS		

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

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RESPONSE

This paper is in response to the non-final Office Action mailed September 6, 2023, from the United States Patent and Trademark Office.

Amendments to the claims begins on page 2.

Remarks begin on page 5.

Applicant authorizes any required fee to be charged to Deposit Account No. 604011.

Petitioner Illumina, Inc., EX1002, p. 2091

Amendments to the Claims

Please amend the claims as follows.

1. (Currently Amended) A method for analyzing a target nucleic acid, the method comprising:

providing a sample comprising nucleic acid comprising a target region;

contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes (MIPs) comprising different nucleotide sequences, each MIP comprising a 5' targeting arm, a central region, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region;

converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target region and some comprising the additional flanking nucleic acids;

isolating the plurality of circularized probes; and

analyzing the target region.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

4. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, different than the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

5-67. (Canceled)

Petitioner Illumina, Inc., EX1002, p. 2092

68. (Previously Presented) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized on either side of the target region, are separated by a plurality of nucleotides on the nucleic acid.

69. (Previously Presented) The method of claim 1, wherein the target region comprises at least 50 base pairs of DNA

70. (Previously Presented) The method of claim 1, wherein each target region is captured by at least three different MIPs.

71. (Previously Presented) The method of claim 70, wherein the step of analyzing the target region comprises sequencing the copy of the target and the additional flanking nucleic acids to generate sequence reads.

72. (Previously Presented) The method of claim 71, wherein the sequencing is next generation sequencing.

73. (Currently Amended) The method of claim 72, wherein the step of analyzing comprises averaging the nucleotide base-composition of[[f]] the sequence reads from the at least three different MIPs.

74. (Previously Presented) The method of claim 1, wherein the plurality of MIPs include at least a first MIP that includes a primer-binding region that can be used to sequence the target region.

75. (Previously Presented) The method of claim 1, wherein each of the plurality of MIPs include a unique differentiator tag sequence.

76. (Cancelled)

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Remarks

With entry of this amendment, claims 1, 3, 4, and 68-75 are pending, with claim 1 being the only independent claim. Claims 1 and 73 are amended to correct typographical issues. Claim 76 is cancelled. No new matter is added.

Rejections under 35 U.S.C. §112

The Office Action, at page 3, states that claim 76 is rejected under 35 U.S.C. 112 (pre-AIA), second paragraph, as indefinite where "less than about 0.05" in claim 76 is indefinite.

Claim 76 is cancelled, rendering the rejection moot and overcome.

Rejections under 35 U.S.C. §103

The Office Action on page 4 states that claims 1, 68, 70-71, and 75-76 are rejected under §103 over Daly, 2007, Clin Chem 53(7):1222-1230, Hardenbohl, 2005, Gen Res 15:269-275, Nilsson, 2006, Trends Biotech 24(2):83-88, US 2007/0212704 to Dong, Streit, 2003, Mol Genet Metab 78(4):259-264, Mockler, 2005, Genomics 85:1-15, Jares, 2006, Clin Trans Oncol 8(3):161-172, WO 95/11995 to Chee, and Johnson, 2005, Trends Gen 21:93-102. On page 15, claims 1, 3-4, 68-71, and 74-76 are so rejected over Krishnakumar, 2008, PNAS 105:9296-9301, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, Johnson, Blasczyk, 1996, Tiss Antigens 47:102-110), and Kotsch, 1999, Tiss Antigens 53:486-497. On page 26, claims 73-73 are so rejected over Krishnakumar, Nilsson, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, Johnson, Blasczyk, Kotsch, and Chaisson, 2004, Bioinformatics 20:2067-2074.

The claims are not obvious.

A determination of obviousness requires basic factual inquiries into the scope and content of the prior art as well as the differences between the claimed invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). When a patent claim includes a limitation that is wholly missing from the prior art, then that prior art does not support a conclusion of obviousness. *Arendi S.A.R.L. v. Apple, Inc.*, 832 F.3d 1355, 1366-67 (Fed. Cir. 2016).

Independent claim 1 recites a method for analyzing a target nucleic acid. As recited, the method includes contacting a target region in a nucleic acid with a plurality of MIPs. The claim

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states that each of the plurality of MIPs captures at least the target region. Further, some of the MIPs also capture additional sequence flanking the target.

That is, for a target region, claim 1 requires multiple MIPs that redundantly capture the target region. Some of those MIPs capture the target region plus additional sequence.

Claim 1 cannot be obvious because the prior art lacks any teaching or suggestion of redundant target capture with MIPs—multiple MIPs in one set that all capture the same target (with some of those capturing additional sequence by the target).

Daly, Hardenbol, Nilsson, and Krishnakumar are the only cited references that even mention MIPs (Dong, Streit, Mockler, Jares, Chee, Johnson, Blasczyk, Kotsch, and Chaisson do not mention MIPs).

Daly reports the use of MIPs to assay genetic variants in genes involved in drug metabolism. *Daly, Abstract*. Daly states that they apply the MIP technology cited in the Hardenbol reference. Id., 1223. Daly explicitly says that "a single best probe design for each locus" was chosen with only "a single probe for each variant." *Daly. 1224*.

Hardenbol reports the use of MIP technology and four-color, single-array detection in genotyping 12,000 SNPs per reaction for studies of genetic association and linkage disequilibrium. *Hardenbol, Abstract.* For SNP detection, Hardenbol states that a probe with hybridizes to a target with abutting ends, which "leaves a single base gap at the location of the SNP". *Id., 270*. Hardenbol states that the probe is tested in four reactions, each with a single dNTP in which successful polymerization and ligation provide allelic differentiation.

From that explanation, it is clear that the MIPs—as understood by Daly and Hardenbol—can each only identify a single base. Because each MIP in Daly and Hardenbol can only interrogate a single base, and there cannot be multiple MIPs for each target.

In fact, each of Daly and Hardenbol explicitly acknowledge and recite that limitation. Daly states that the assay uses "a single probe for each variant." *Daly. 1224*. Hardenbol states that the assay uses "only a single probe per SNP." *Hardenbol, 272*.

Nilsson only reports also MIPs that can interrogate a single base. Nilsson reviews technologies that use specific DNA circularization coupled to DNA amplification and states that padlock probes and MIPs provide parallel, high throughput single nucleotide polymorphism (SNP) genotyping. *Nilsson, Abstract*. Nilsson states that the MIP assay has been applied to a 12,000 SNP multiplex genotyping project, citing the Hardenbol reference. *Id., 84*. Nilsson

reports that each "SNP is positioned between the ends of the padlock probe creating a single-nucleotide gap in the probe-target hetero-duplex." *Nilsson, 84, caption to Figure 1.*

Krishnakumar reports using long padlock probes (LPPs) (probes >300 bases in size) to amplify and analyze sequences of up to 50 bases in length, in parallel. *Krishnakumar, Abstract.* Krishnakumar reports that, as long as one excludes exons for which primers would require a BsaI or an MlyI site, the LPPs are useful for the simultaneous multiplex amplification of DNA sequences in a single tube for targets that can range from <100 to 500 bp. *Id., 9298, 9299.* Krishnakumar does not teach or suggest multiple different probes that capture the same target.

A significant feature of claim 1 that cannot be accomplished by anything taught in Daly, Hardenbol, Nilsson, and Krishnakumar is the redundant capture and amplification of an unknown target sequence by multiple MIPs. Those references say nothing suggesting that multiple different MIPs could capture the same target. In fact, in Daly, Hardenbol and Nilsson, because each MIP can only capture a single base, the MIPs as understood from those references could not even be used to perform the claimed method.

Dong, Streit, Mockler, Jares, Chee, Johnson, Blasczyk, Kotsch, and Chaisson do not mention MIPs and do not cure the deficiencies of Daly, Hardenbol, Nilsson and Krishnakumar.

Dong only reports methods for amplifying target nucleic acids while reducing non-specific fluorescence and undesired amplification products, using enzyme inhibitors that comprise a nucleotide sequence and at least one quencher. *Dong, Abstract.* Dong states that amplification may include padlock versions of ligase-mediated amplification. *Id., [0109].* Dong states that a DNA fragment may include a plurality of different target nucleic acids and that a given target nucleic acid may overlap another target nucleic acid. *Id., [0087].* Dong is using the word "target" differently than in the present claims. Dong uses target to refer to where probes will anneal, i.e., the binding sites. Dong does not disclose any probe that can capture (i.e., make copies of for sequencing) overlapping targets.

Streit reports mutation detection in the CFTR gene. *Streit at Abstract and 261, Table 2.* Streit simply reports amplifying regions of the CFTR gene. *Id. at 260.* There are no MIPs in Streit and, in Streit there is no target that is captured by multiple probes.

Mockler is a review article on microarray tiling experiments. *Mockler Abstract.* Mockler does not disclose the use of MIPS. The probes are each oligonucleotides designed against a known or predicted reference genome. There is no probe in Mockler that is circularized. There is

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no probe that is used to capture unknown target sequences. Rather, the sequence being detected needs to already be known. These probes are not MIPS. Moreover, only one probe is used for any target (i.e., no redundant capture of 1 target by multiple different probes).

Jares, like Mockler, is also a review article comparing microarray tiling experiments of gene expression and DNA copy number. *Jares. Abstract.* The probes in Jares are not MIPS. Each probe is designed against a reference genome. For SNP detection, Jares uses two probes: one specific to the SNP, and one specific to wild-type. *Id., 167.* The probes do not detect unknown bases between targeting arms. These probes are not MIPS. Moreover, only one probe binds to any target, depending on the base present.

Chee only reports chips of immobilized probes useful for comparing a reference polynucleotide sequence of known sequence with an, e.g., mutant target sequence. *WO 95/11995, Abstract*. If fact, Chee is one of the original reports of the Affymetix DNA microarray sold as GeneChip. The DNA microarray is wholly unlike the present claims both in what "tiling" means and in how information is read. In Chee, tiling refers to probes in adjacent cells in an array on a chip differs from its neighbor by the nucleotide at an interrogation position. *Id., page 11, lines 21-26*. In Chee, the presence of a target is read by labeling DNA targets, before hybridization to the probe array, with fluorescein. *Id., page 117, lines 32-36*. Specifically, for preparation of the labeled sample, genomic DNA is amplified by PCR followed by linear amplification with dA, dC, dG, and fluorescein dUTP before hybridization to the array. *Id., page 124, lines 26-31; page 126, lines 1-5*. There are no MIPs in Chee, no probes that "capture" unknown target, and no targets that are captured "redundantly", by more than one probe.

Johnson, like Mockler and Jares, reports microarray tiling experiments of gene expression. *Johnson, Abstract.* The probes discussed in Johnson are not MIPS. The probes are oligonucleotides designed against a known or predicted reference genome. *Id., at 93.* The probes do not covalently-close to detect unknown bases between targeting arms. Rather, the sequence being detected needs to already be known. These probes are not MIPS.

Blasczyk reports only the improvements to PCR products to overcome the limitations of Sanger sequencing. *Blasczyk, 102-103.* Blasczyk reports the use of two additional primers to capture the 5' and 3' ends of a target nucleic acid, typically lost during Sanger sequencing. Blasczyk clarifies that "the use of a nested approach requires the stocking of large amounts of sequencing primers. Hence, the application of dye primer sequencing techniques becomes

infeasible." *Id., 103.* Kotsch (like Blasczyk) seeks to overcome drawbacks in PCR strategies that "that do not allow sequence analysis of the 5' and 3' ends of the 2nd exon" in HLA-DRB genes. *Kotsch, 487.* Kotch reports the use of three nested primers that correspond to three variants of a conserved region in the 3' end of intron 1 of the HLA-DRB gene. *Id., 488.* Chaisson reports only that new computer-assisting assemblies may facilitate assembling short reads together, for example from pyrosequencing reads. *Chaisson, 2067-68.*

Factual analysis reveals that the prior art does not teach or suggest redundant MIP capture of an unknown target sequence. There is no prior disclosure of MIP strategies that capture each target redundantly with multiple different MIPs.

Because the asserted prior art does not teach or suggest multiple MIPs that redundantly capture the same target region and in which some of the MIPs in the probe set also capture additional nucleic acids flanking the target region, as recited in independent claim 1, claim 1 is not obvious. Because the only independent claim is not obvious, none of the claims are obvious.

The rejections under §103 should be withdrawn.

Conclusion

Applicant submits that all rejections have been addressed and overcome. Applicant requests a Notice of Allowance.

Dated December 6, 2023

Respectfully submitted,
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Petitioner Illumina, Inc., EX1002, p. 2098

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
13/266,862	**12/13/2023 11:53:32 AM Z ET**	**MLB-002/01US 34468/8**

Title of Invention

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	6082	FILED BY	Sandra Richards
PATENT CENTER #	63595119	FILING DATE	03/13/2012
CUSTOMER #	179511	FIRST NAMED INVENTOR	Gregory Porreca
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Thomas Meyers

Documents

TOTAL DOCUMENTS: 4

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
MLB-002-01US-Corr-ADS-Ltr-121323.pdf	1	Request for Corrected Filing Receipt	70 KB
Molecular-Loop-POA-010923.pdf	2	Power of Attorney	165 KB
MLB-002-01US-CADS-121323.pdf	6	Application Data Sheet	134 KB
Warning: This is not a USPTO supplied ADS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
MLB-002-01US-373c-	3	Assignee showing of ownership	123 KB

statement.pdf	per 37 CFR 3.73

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
MLB-002-01US-Corr-ADS-Ltr-121323.pdf	6AFF9174308D3AC612DA03409E6FC12BD924DF41A91EC621F5DA497931E53D82A061392C96DC883F59CCE37FE918D0646251EE9AC59751E14E51B1387A402CBE
Molecular-Loop-POA-010923.pdf	B07224BD4BBD44B11BF19438B50A8572EEF75942AF72796BEAD4DF6E0EAB42A798180506FFA785099A78CBA014E43ABBD0DEA8D3E0E1ACA9E0BFC14FE4DE8FF9
MLB-002-01US-CADS-121323.pdf	8CA4E211E3A4E47423B96463414C3682A52093D78D24951BA2DEEE7AB50A766683B014D66506E3B9FB404A5ED5225C59008F65ED59D65EA2517FC7A78B85024A
MLB-002-01US-373c-statement.pdf	2A031EB5FE92FCB7D546D1D88D204A4F767E4C9CDA5F67F241CBEDC82646A7D38C5CC1DFB30B0A7FCA02D38FD78DA434D03D9982F33A484E799F5B1D7A9B1FE3

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 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-002/01US 1006120/9

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosciences, Inc.		
APPLICATION NO.:	13/266,862	ART UNIT:	1634
FILING DATE:	March 13, 2012	CONF. NO.:	6082
EXAMINER:	Steven C. Pohnert		
TITLE:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS		

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

FILED ELECTRONICALLY

CORRECTED APPLICATION DATA SHEET

A Corrected Application Data Sheet (ADS) is submitted herewith to remove --Molecular Loop Biosolutions, LLC-- as non-Applicant assignee and to update the named Applicant to Molecular Loop Biosciences, Inc. Applicant submits here with a 3.73 statement showing chain of title to, and a Power of Attorney in the name of, Molecular Loop Biosciences, Inc.

Applicant requests a Corrected Filing Receipt showing the change. Applicant believes that no fee is due for entry of the Corrected ADS but authorizes any required fee to be charged to Deposit Account No. 604011.

Dated December 13, 2023

Respectfully submitted,
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PTO/AIA/80 (07-17)
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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: 179511

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: 179511

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Molecular Loop Biosciences, Inc.
300 Tradecenter, Suite 5400, Woburn, MA 01801

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	Date09-Jan-2023
NameGregory Porreca	Telephone978-254-7799
TitlePresident 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.**
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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.

Supplemental Application Data Sheet

Application Information

Application number::	13/266,862
Filing Date::	03/13/12
Application Type::	Regular
Subject Matter::	Utility
Suggested classification::	435/006.100
Suggested Group Art Unit::	1634
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::	~~MLB-002/01US 34468/8~~ MLB-002/01US 1006120/9
Request for Early Publication?::	No
Request for Non-Publication?::	No
Small Entity?::	Yes
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

Applicant Information

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Petitioner Illumina, Inc., EX1002, p. 2104

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Petitioner Illumina, Inc., EX1002, p. 2106

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Representative Information

Representative Customer Number::	~~21710~~ 179511

Petitioner Illumina, Inc., EX1002, p. 2107

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::	Prior Appl Status::
This Application	a 371 of international	PCT/US10/01293	04/30/10	
PCT/US10/01293	Claims benefit of provisional	61/182089	05/28/09	Expired
PCT/US10/01293	Claims benefit of provisional	61/179358	05/18/09	Expired
PCT/US10/01293	Claims benefit of provisional	61/178923	05/15/09	Expired
PCT/US10/01293	Claims benefit of provisional	61/174470	04/30/09	Expired

Foreign Priority Information

Assignee Information

Assignee name::	~~Molecular Loop Biosolutions, LLC~~ Molecular Loop Biosciences, Inc.
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City of mailing address::	Cambridge
State or Province of mailing address::	MA
Country of mailing address::	US
Postal or Zip Code of mailing address::	02138

Petitioner Illumina, Inc., EX1002, p. 2108

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.			
Signature	/Thomas C. Meyers/	Date	December 13, 2023
Name	Thomas C. Meyers	Registration No.	36,989

63213991 v1

Petitioner Illumina, Inc., EX1002, p. 2109

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Molecular Loop Biosciences, Inc.

Application No./Patent No.: 16/266862 Filed/Issue Date: March 13, 2012

Titled: METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Molecular Loop Biosciences, Inc., 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. ☑ 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. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Good Start Genetics, Inc.

   The document was recorded in the United States Patent and Trademark Office at

   Reel 027860, Frame 0025, or for which a copy thereof is attached.

2. 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.

This collectionof information is required by 37CFR 3.73(b). The informationis required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application.Confidentiality isgoverned by 35U.S.C. 122 and37 CFR 1.11and 1.14.This collection is estimated to take 12 minutes to complete, including gathering,preparing, and submitting the completed applicationform 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 besent 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 COMPLETEDFORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA22313-1450** .

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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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: Molecular Loop Biosolutions, LLC To: Molecular Loop Biosciences, Inc.

The document was recorded in the United States Patent and Trademark Office at
Reel 058263, Frame 0673, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
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5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
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6. From: _____ To: _____

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/	December 13, 2023
Signature	Date
Thomas C. Meyers	36,989
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requiresthat you begiven certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirementsof the Act, please be advised that: (1)the general authority for the collectionof this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary;and (3) the principalpurpose for whichthe informationis used by the U.S. Patent and Trademark Office is to process and/or examine your submission related toa patent application or patent. If you do not furnishthe requested information, the U.S. Patent and Trademark Officemay not be able to process and/or examine yoursubmission, which may result in termination of proceedings orabandonment of the application or expiration of the patent.

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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)).
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.
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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
13/266,862	03/13/2012	1634	1540	MLB-002/01US 1006120/9	39	3

CONFIRMATION NO. 6082

REPLACEMENT FILING RECEIPT

179511
Withers Bergman LLP
101 Federal Street, Suite 1900
Boston, MA 02110

OC000000065910826

Date Mailed: 12/18/2023

Receipt is acknowledged of this non-provisional utility 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 FIRST INVENTOR, 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 corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction 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 provided that the request is grantable.

Inventor(s)

Gregory Porreca, Cambridge, MA;
Uri Laserson, Boston, MA;
Jin Billy Li, Medford, MA;
E. Robert Wassman, Marblehead, MA;

Applicant(s)

Gregory Porreca, Cambridge, MA;
Uri Laserson, Boston, MA;
Jin Billy Li, Medford, MA;
E. Robert Wassman, Marblehead, MA;

Assignment For Published Patent Application

Molecular Loop Biosciences, Inc., Cambridge, MA

Power of Attorney: The patent practitioners associated with Customer Number 179511

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/US10/01293 04/30/2010
which claims benefit of 61/174,470 04/30/2009
and claims benefit of 61/174,923 05/01/2009
and claims benefit of 61/179,358 05/18/2009
and claims benefit of 61/182,089 05/28/2009

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.

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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: No

Permission to Access Search Results: No

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: 03/19/2012
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/266,862**
Projected Publication Date: 06/28/2012
Non-Publication Request: No
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.

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

Petitioner Illumina, Inc., EX1002, p. 2114

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

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NOT GRANTED

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Petitioner Illumina, Inc., EX1002, p. 2116

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 1006120/9

CONFIRMATION NO. 6082

179511
Withers Bergman LLP
101 Federal Street, Suite 1900
Boston, MA 02110

POA ACCEPTANCE LETTER

OC000000065910784

Date Mailed: 12/18/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/13/2023.

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**.

/dtdinh/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/266,862	03/13/2012	Gregory Porreca	MLB-002/01US 1006120/9	6082

179511 7590 02/15/2024

Withers Bergman LLP
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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
02/15/2024	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):

Samantha.Metcalf@withersworldwide.com
US.Docketing@withersworldwide.com
kristina.scandore@withersworldwide.com

Office Action Summary	**Application No.** 13/266,862	**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 12/6/2023.

☐ 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) 1,3-4 and 68-75 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) 1,3-4 and 68-75 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., EX1002, p. 2119

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. 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 12/6/2023.

Claims 1, 3-4,68-75 are pending.

Claims 2, 5-67, 76 have been canceled.

Claims 1, 3-4 and 68-75 are being examined.

The 112(b) was been withdrawn in view of the amendment to cancel claim 76.

Priority

The instant application was filed 3/13/2012 and is a national stage entry of PCT/US10/01293 filed 4/30/2010 and claims priority to provisional application 61/147,470 filed 4/30/2009; provisional application 61/147923 filed 5/1/2009; provisional application 61179358 filed 5/18/2009; and 61/182,089 filed 5/28/2009.

Claim Rejections - 35 USC § 103

2. 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.

3. Claim 1, 68, 70-71, 75-76 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Daly (Clinical Chemistry (2007)volume 53, pages 1222-1230), Hardenbohl (Genome Research (2005) volume 15, pages 269-275), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metabolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102).

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of capture is not defined by the specification. Thus the broadest reasonable interpretation is allowing hybridization or isolation (consistent with page 7-8 of the specification).

The prior art of record exemplifies that MIP and their analysis was known. MIPs with overlapping sequences were known, as were methods of tiling. Thus the claims are nothing more than the predictable combination of known steps and elements as exemplified below.

Daly teaches, " Molecular inversion probe (MIP) technology is an oligonucleotide-based method that can be used to analyze several thousand SNPs in a single assay (20). This technique has been used extensively for the HapMap project (21) and offers several advantages for multiplex genotyping. First, PCR amplification occurs after mutation detection, at which time MIPs have been converted to standard-length oligonucleotides of similar sequence composition utilizing common PCR primers. Second, the MIPs are designed to be locus-specific rather than allele specific and require only a single probe per marker, so any loss of performance of a probe will affect both alleles equally, avoiding unbalanced genotyping. Third, each probe has two recognition sequences as in PCR but retains unimolecular hybridization kinetics, enabling high multiplexing with low concentration requirements. Finally, the use of molecular tag sequences on the probes allows hybridization to the microarray to be independent of the gene sequence, increasing the specificity and sensitivity of detection and allowing for a high degree of flexibility in assay design (22)." (page 1223, 1st column top).

Daly continues, " We have applied MIP technology to develop an assay testing 1227 variants in 169 genes involved in drug metabolism. Within this set, we have chosen a core set of 165 variants in 27 genes for extensive analytical validation." (page 1223, 1st column, 2nd full paragraph).

Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd

column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T.

Daly does not teach the sequence of the probes or specifically teach probes with additional flanking region.

Nilsson teaches MIP, padlock probes and selector probes all are circularized by hybridization to target nucleic acids to target nucleic acids (Figure 1 and figure 2, throughout). Nilsson teaches the padlock probes use ligation, while MIPs and selector probes use gap filing and ligation (83, bottom 2nd column-85). Nilsson teaches the probes which are ligated are separated from non-closed probes by digestion (isolation). Nilsson in figure 3 demonstrates amplification of circularized probes. Nilsson teaches, "Currently, 12 000 MIPs can be amplified and analyzed in parallel. We expect that a similar, or greater, number of selector probes can be applied to amplify large sets of genomic DNA fragments for subsequent analysis using high-throughput sequencing technologies [24,25]. Much effort is being invested into developing low-cost sequencing methods with the ultimate goal of sequencing an entire human genome for $1000 [5]. A more realistic goal, in the shorter term, is to sequence only the interesting parts of the genome, for example, all exons: the selector technology could be combined profitably with several of the sequencing techniques to achieve this." (bottom 1st column page 87, top of 2nd column).

Nilsson concludes, "Detailed understanding of multicellular organisms and many human diseases will ultimately require analyses of individual cells in their natural tissue environment."(page 87, 2nd column 1st full paragraph).

Thus Nilsson suggest examination of human nucleic acids samples by use of circular probes including padlock, MIP and selector probes which are circularized by hybridization, isolation, amplifying and sequencing to characterize disease states by the genetic status.

Nilsson does not specifically teach the use of overlapping probes or targeting overlapping sequences

Hardenbohl (Genome Research (2005) volume 15, pages 269-275) teaches, " Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

Chee et al (WO 95/11995) teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays to determine nucleic acid sequences (see Figure7 and page 37 line 10- page 38 line 34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and a target sequence for the identification of single base mutants possible in the

reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (see page 18, lines 1-8). Chee teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-6). Chee teaches the probes are immobilized on an array. Chee teaches, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences' (page 32).

Johnson teaches, "The first genomic-scale study of transcription using microarrays was performed in Escherichia coli using probes 'tiled' at regular intervals (Box 1) to provide an unbiased view of transcription with respect to the locations of known and predicted genes [12"

Dong teaches methods and kits for amplification of target nucleic acids(abstract). Dong teaches the method before or in conjunction with sequencing (0115). Dong teaches some embodiments include amplification with ligase mediated amplification techniques including padlock probes (0109). Dong in 0087 teaches, "In some embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both."

Mockler teaches the use of tiling arrays to examine the whole genome including overlapping and nonoverlaping (figure 1).

Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165)

Streit teaches the CFTR gene has multiple mutations in close proximity in exon 11 (table 2) (s549Nm G542X, G551D and R553X).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use overlapping circularized probes such as MIPs, padlock or selector probes using overlapping probes each have different nucleic acid arm sequences and thus capture additional flanking sequences. The artisan would be motivated to use to detect specific mutations as the art teaches MIPs that are overlapping and demonstrates the use of MIP to detect previously unknown transcripts.. The artisan would have a reasonable expectation of success as the artisan is merely designing and circularized probes such as MIPs, padlock or selector probes to detect known mutations by known means.

Daly does not specifically converting to a closed circularized probe , isolating and analyzing.

However, Daly in the first cited paragraph references Hardenbohl (reference 20).

Hardenbohl teaches., "single oligonucleotide probe with recognition sequences at each terminus is hybridized with a genomic target sequence such that it forms a circular structure, with the ends of the probe abutting. This leaves a single base gap at the location of a SNP. This gapped-duplex is then tested in four separate reactions, each with a single dNTP species present, in which successful polymerization/ligation provides

allelic differentiation. The probes are subsequently released from the genomic DNA and those that have been covalently circularized in the correct allele/nucleotide reaction combinations are amplified using a "universal" PCR primer pair. Each amplified probe contains a unique tag sequence that is complementary to a sequence on the universal tag array. Tags have been selected to have a similar Tm and base composition and to be maximally orthogonal in sequence complementarity. Amplicons are fluorescently labeled and the tag sequences released from the genome homology regions using a restriction endonuclease treatment. The tags are then detected using a complementary tag array." (MIP technology, page 270).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to circularize, isolate and analyze the MIP and target region. The artisan would be motivated as Daly specifically references Hardenbohl. The artisan would have a reasonable expectation of success as the artisan is using art accepted probes in an art accepted manner.

With regards to claim 68, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that the detection of an insertion by a probe designed to detect a SNP would have a separation of a plurality of nucleotides (the insertion in addition to the SNP). The artisan would be motivated as Daly suggest the detection of insertions. The artisan would have a reasonable expectation of success as the artisan is using known probes by known methods.

With regards to claim 70, Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the

microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different.

With regards to claim 71, Hardenbohl teaches sequencing (674, 2nd column-675). Daly teaches sequencing (figure 1A).

With regards to claim 75-76, Hardenbohl teaches., "Each amplified probe contains a unique tag sequence …." (MIP technology, page 270).

Response to Arguments

The response traverses the rejection asserting, "Claim 1 cannot be obvious because the prior art lacks any teaching or suggestion of redundant target capture with MIPs-multiple MIPs in one set that all capture the same target (with some of those capturing additional sequence by the target).". This argument has been thoroughly reviewed but is not considered persuasive as Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different. Further, Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T. Further, the art as a whole demonstrates the use of tiling arrays to capture regions or targets of interest. Thus using MIPs that tile across a target of interest renders this limitation obvious.The response continues by asserting, "Daly reports the use of MIPs to assay genetic variants in genes involved in drug metabolism. Daly, Abstract. Daly states that they

apply the MIP technology cited in the Hardenbol reference. Id., 1223. Daly explicitly says that "a single best probe design for each locus" was chosen with only "a single probe for each variant." Daly. 1224." his argument has been thoroughly reviewed but is not considered persuasive as Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T in addition to the normal sequences targeted by the MIPs.

The response continues by asserting, "From that explanation, it is clear that the MIPs-as understood by Daly and Hardenbol can each only identify a single base. Because each MIP in Daly and Hardenbol can only interrogate a single base, and there cannot be multiple MIPs for each target." The response appears to be indicating the MIPs are to a single nucleotide. This argument has been thoroughly reviewed but is not considered persuasive as the specification teaches, 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)." This interpretation is inconsistent with the teachings of the specification.

The response continues by providing the representatives opinion of the Krishnakumar. This is noted. The response continues by asserting, "n 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)." This argument has been thoroughly reviewed but is not considered persuasive s Daly teaches, "Each locus is measured in 3 well-separated features on the microarray, providing internal redundancy to reduce the chance of genotyping failure resulting from localized errors such as debris on the microarray." (page 1223, 2nd column-1224) Thus Daly demonstrates at least 3 probes were used to examine each locus, as the probes are on different portions of the microarray they are different. Further, Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T. Further, the art as a whole demonstrates the use of tiling arrays to capture regions or targets of interest. Thus using MIPs that tile across a target of interest renders this limitation obvious.The response continues by asserting, "Daly reports the use of MIPs to assay genetic variants in genes involved in drug metabolism. Daly, Abstract. Daly states that they apply the MIP technology cited in the Hardenbol reference. Id., 1223. Daly explicitly says that "a single best probe design for each locus" was chosen with only "a single probe for each variant." Daly. 1224." his argument has been thoroughly reviewed but is not considered persuasive as Daily teaches in supplemental table 1 insertions were detected for CYP2D6star21_2573insC_2, O2Ins1589T in addition to the normal sequences targeted by the MIPs.

The response of 10/17/2022 concedes Jares teaches another review article on tiling arrays, but does not teach MIPS. This argument has been thoroughly reviewed but is not considered persuasive as Jares teaches, "The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed

identifying transcriptional activity on previously unannotated regions of the genome." (page 164-165) The response provides no arguments to the use of tiling strategies in the design of MIPs which allow for inclusion of additional flanking sequences.

The response of 10/17/2022 continues by conceding Chee also teaches methods of designing tiling probes which allow for the inclusion of additional flanking sequences in probe design, but asserts the teachings are limited to multiple probes to interrogate a different base. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not exclude multiple different MIPS to examine a single base. Further the tiling allows for additional flanking sequences in addition to the single base.

The response of 10/17/2022 concedes Johnson teaches a probes of a microarray tiled across sequences of interest to detect gene expression of known sequences. The response asserts the tiling probes of Johnson to not detect unknown bases. This argument has been thoroughly reviewed but is not considered persuasive as the claims do not require the capture of unknown bases.

The response of 10/17/2022 concludes arguments by asserting the art of Dong, Streit, Mockler, Jares, Chee, Johnson do not teach MIPs. There is no evidence of unpredictability or unexpected results of using known strategies of probe design in the design of MIPs . Thus the rejection is maintained.

Thus the rejection is maintained.

4. Claim 1, 3-4, 68-71, 74-76 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105, pages 9296-9301), Nilsson (Trends in Biotechnology (2006) volume

24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metabolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Hardenbohl (Genome Research (2005) volume 15, pages 269-275) Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102)Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)

MPEP 2111 states:

> The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."

MPEP 2111.01 states

> Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim.

It is noted that the specification lacks a limiting definition of a molecular inversion probe. Thus "molecular inversion probe" is being given the broadest reasonable interpretation in view of the claims and consistent with the art as a probe with a 5' targeting arm, central region and 3' targeting arm and allows for formation of a circle upon hybridization.

Claim 1 has been amended to recite, "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 on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region" The specification does not teach a limiting definition of target. However the specification states, "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)." Thus the broadest reasonable interpretation of a target region is a nucleotide. Further the recitation of "a target" allows for the interpretation of more than one target in a contiguous sequence.

Further the recitation of capture is not defined by the specification. Thus the broadest reasonable interpretation is allowing hybridization or isolation (consistent with page 7-8 of the specification).

The prior art of record exemplifies that MIP and their analysis was known. MIPs with overlapping sequences were known, as were methods of tiling. Thus the claims are nothing more than the predictable combination of known steps and elements as exemplified below.

Krishnakumar teaches, "As a proof of principle, we used SMART technology to simultaneously amplify 485 human exons ranging from 100 to 500 bp from human genomic DNA. In multiple repetitions, >90% of the targets were successfully amplified with a high degree of uniformity, with 70% of targets falling within a 10-fold range and all

products falling within a 100-fold range of each other in abundance. We used long padlock probes (LPPs) >300 bases in length for the assay, and the increased length of these probes allowed for the capture of human sequences up to 500 bp in length, which is optimal for capturing most human exons. To engineer the LPPs, we developed a method that generates ssDNA molecules with precise ends, using an appropriately designed dsDNA template. The template has appropriate restriction sites engineered into it that can be digested to generate nucleotide overhangs that are suitable for lambda exonuclease digestion, producing a single stranded probe from dsDNA. The SMART technology is flexible and can be easily adapted to multiplex tens of thousands of target sequences in a single reaction.."

Krishnakumar teaches, " In a series of singleplex assays, padlock probes that were 120 bases in length were annealed to human DNA, and the gap-fill reaction was performed as described in Materials and Methods using the conditions for the Stoffel DNA polymerase. After completion of the gap-fill reaction with the formation of the circular DNA molecule by ligation, the desired DNA sequences were amplified using common primers flanking the 3' and 5' target sequences of the padlock probe (Fig. 1D). We measured the performance of the assay by running the amplified products on a 2% agarose gel to determine the length of the amplified products. We concluded that the assay was successful and quite reproducible when the length of gap-fill sequences was 200 bases, but we found that the consistency and the reproducibility of the assay diminished as the size of the gap-fill region increased [supporting information (SI) Tables S1 and S2]."

Krishnakumar continues, "To test whether short padlock probes were limiting the gap-fill reaction, we needed to make longer probes. To this end, we developed a methodology for making probes that were 300 bases. We posited that the LPPs should (potentially) overcome the limitations of the smaller-size probes. In our current protocol, the ssDNA probe is produced from a specifically designed dsDNA template using a series of enzymatic reactions and selective removal of one of the strands using lambda exonuclease digestion. We first built the "core" construct of the template that is common to all probes. The core is composed of a common nucleic acid sequence, the spacer, derived from the bacteriophage lambda flanked by the amplification primers (Fig. 1A)."(page 9297, last paragraph).

While Krishnakumar teaches padlock probes (MIPs) to detect different size target sequences, Krishnakumar does not specifically teach the use of MIPs in which one MIP provides additional flanking sequences of the target region.

However, Blasczyk teaches, "Even if sequencing is performed in both directions, the ends of the templates will not yield readable sequencing ladders. Indeed, these problems can be solved by the use of 5' and 3' nested sequencing primers." (page 102 last paragraph-top of page 103).

Kotsch teaches, "The use of nested sequencing primers additionally increased the specificity and quality of the sequencing reactions." (495, 2ND column, bottom)

Nilsson teaches MIP, padlock probes and selector probes all are circularized by hybridization to target nucleic acids to target nucleic acids (Figure 1 and figure 2, throughout). Nilsson teaches the padlock probes use ligation, while MIPs and selector probes use gap filing and ligation (83, bottom 2nd column-85). Nilsson teaches the

probes which are ligated are separated from non-closed probes by digestion (isolation). Nilsson in figure 3 demonstrates amplification of circularized probes. Nilsson teaches, "Currently, 12 000 MIPs can be amplified and analyzed in parallel. We expect that a similar, or greater, number of selector probes can be applied to amplify large sets of genomic DNA fragments for subsequent analysis using high-throughput sequencing technologies [24,25]. Much effort is being invested into developing low-cost sequencing methods with the ultimate goal of sequencing an entire human genome for $1000 [5]. A more realistic goal, in the shorter term, is to sequence only the interesting parts of the genome, for example, all exons: the selector technology could be combined profitably with several of the sequencing techniques to achieve this." (bottom 1st column page 87, top of 2nd column).

Nilsson concludes, "Detailed understanding of multicellular organisms and many human diseases will ultimately require analyses of individual cells in their natural tissue environment."(page 87, 2nd column 1st full paragraph).

Thus Nilsson suggest examination of human nucleic acids samples by use of circular probes including padlock, MIP and selector probes which are circularized by hybridization, isolation, amplifying and sequencing to characterize disease states by the genetic status.

Nilsson does not specifically teach the use of overlapping probes or targeting overlapping sequences

Hardenbohl (Genome Research (2005) volume 15, pages 269-275) teaches, " Probes can target overlapping sequences since the genomic DNA is not saturated with hybridized probe."(p 274, 2nd column, assay design).

Chee et al (WO 95/11995) teaches, "The invention provides a number of strategies for comparing a polynucleotide of known sequence (a reference sequence) with variants of that sequence (target sequences). Chee teaches, "Reference sequences of interest include sequences known to include mutations or polymorphisms associated with phenotypic changes" (page 19). The comparison can be performed at the level of entire genomes, chromosomes, genes, exons or introns, or can focus on individual mutant sites and immediately adjacent bases" (page 18). Chee teaches an array of capture probes (see figure 16,and page 79 lines 23-39) and block tiling arrays to determine nucleic acid sequences (see Figure7 and page 37 line 10- page 38 line 34). Chee teaches the use of immobilized arrays to interrogate a reference sequence and a target sequence for the identification of single base mutants possible in the reference sequence can associated with disease (see page 31 lines 6-7, and page 11 line 9 and 10). Further Chee teaches this approach allows simultaneous detection and quantification of multiple target sequences (see page 32 lines18-19), allowing for sequence determination. Chee teaches a method of mutation detection for analyzing known target sequences for individual mutant sites and immediately adjacent bases (see page 18, lines 1-8). Chee teaches the use of capture probes of 15 to 30 nucleotides, perfectly complementary to the DNA of interrogation (see page 27 lines 2-6). Chee teaches the probes are immobilized on an array. Chee teaches, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences' (page 32).

Johnson teaches, “The first genomic-scale study of transcription using microarrays was performed in Escherichia coli using probes ‘tiled’ at regular intervals (Box 1) to provide an unbiased view of transcription with respect to the locations of known and predicted genes [12”

Dong teaches methods and kits for amplification of target nucleic acids(abstract). Dong teaches the method before or in conjunction with sequencing (0115). Dong teaches some embodiments include amplification with ligase mediated amplification techniques including padlock probes (0109). Dong in 0087 teaches, “In some embodiments, a given target nucleic acid can overlap one target nucleic acid on its 5'-end, another target nucleic acid on its 3'-end, or both.”

Mockler teaches the use of tiling arrays to examine the whole genome including overlapping and nonoverlaping (figure 1).

Jares teaches, “The use of whole genome tiling arrays, composed of millions of non overlapping or partially overlapping probes, tiled to cover whole chromosomes or the entire genome in an unbiased approach, has allowed identifying transcriptional activity on previously unannotated regions of the genome.” (page 164-165)

Streit teaches the CFTR gene has multiple mutations in close proximity in exon 11 (table 2) (s549Nm G542X, G551D and R553X).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use overlapping circularized probes such as MIPs, LPPs, padlock or selector probes using overlapping probes each have different nucleic acid arm sequences and thus capture additional flanking sequences and sequencing the MIP. The artisan would be motivated to use to detect specific mutations

as the art teaches MIPs that are overlapping and demonstrates the use of MIP to detect previously unknown transcripts.. The artisan would have a reasonable expectation of success as the artisan is merely designing and circularized probes such as MIPs, padlock or selector probes to detect known mutations by known means.

With regards to claim 3-4, It would have been prima facie obvious to one of skill in the art prior at the time the invention was made that design padlock probes to detect fragments of 500 nucleotides the 3' and 5' targeting arms would not overlap have different sequences than padlock probes for detection of 200 nucleotides. The artisan would be motivated to provide targeting arms that are long enough to target the 200 or 500 nucleotide sequence without the expense of making them extremely long.

With regards to claim 68-69, Krishnakumar teaches MIPS with 2580-500 nucleotides in target region (figure 2).

With regards to claim 70, Krishnakumar teaches the use of 50 attomoles of the probes. Thus Krishnakumar teaches at least 2 different MIPS.

With regards to claim 74, Krishnakumar teaches, ", the desired DNA sequences were amplified using common primers flanking the 3' and 5' target sequences of the padlock probe (Fig. 1D)."

With regards to claim 75-76, Hardenbohl teaches., "Each amplified probe contains a unique tag sequence …." (MIP technology, page 270).

Response to Arguments

The arguments to the instant rejection are addressed above.

5. Claims 72-73 rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Krishnakumar (Proceedings National Academy of Sciences (2008) volume 105,

pages 9296-9301), Nilsson (Trends in Biotechnology (2006) volume 24, pages 83-88), Dong (USPGPUB20070212704), Streit (Molecular Genetics and Metolism (2003) volume 259-264) Daly (Clinical Chemistry (2007) volume 53, pages 1222-1230) (IDS 7/1/2021), Hardenbohl (Genome Research (2005) volume 15, pages 269-275) Mockler (Genomics (2005) volume 85, pages 1-15), Jares (Clin Trnal Oncology (2006)0 volume 8, pages 161-172), Chee et al (WO 95/11995), Johnson (Trends in Genetics (2005) volume 21, pages 93-102)Blasczyk (Tissue Antigens (1996) volume 47, pages 102-110), Kotsch (Tissue Antigens (1999) volume 53, pages 486-497)) as applied to claim 1, 3-4, 68-71 above, and further in view of Chaisson (Bioinformatics (2004) volume 20, pages 2067-2074)

The teachings of Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee et al, Johnson, Blasczyk, Kotsch are set forth above.

While Krishnakumar, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee et al, Johnson, Blasczyk, Kotsch teach sequencing of padlock probes (MIPs), they do not specifically teach next generation sequencing or averaging sequence reads from at least 3 MIPS.

However, Chaisson teaches fragment assembly for short reads including 454 Life Sciences sequencer ((2067, 2nd column, 1st paragraph).. Chaisson teaches the next generation sequencing allow for greater coverage at a lower cost than Sanger sequencing. Chaisson teaches different methods of different read lengths (2067, 2nd column, 1st paragraph). Chaisson teaches determining average read length (page 2069, 2nd column bottom).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the arms of the MIPS and determine average read length. The artisan would be motivated to increasing the speed and coverage of sequencing while reducing the cost. The artisan would have a reasonable expectation of success as the artisan is using known methods of detecting sequences and determining average read length.

Response to Arguments

The response traverses the rejection asserting the art does not teach the use of different MIPs having different nucleic acid sequences to capture the same target region. This argument has been thoroughly reviewed but is not considered persuasive as the art demonstrates the capture of additional flanking sequences by insertions with MIPs as well as tiling arrays. Thus this limitation is obvious over the art in view of the breadth of the claims.

Summary

No claims are allowed.

Conclusion

1. **THIS ACTION IS MADE FINAL.** 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.

2. 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 Monday- Friday about 6:00 AM-5:00 PM, 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, Winston Shen can be reached on 571-272-3157. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven Pohnert/
Primary Examiner, Art Unit 1634

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PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
13/266,862	**06/14/2024 11:04:51 AM Z ET**	**MLB-002/01US 1006120/9**

Title of Invention

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	6082	FILED BY	Kristina Scandore
PATENT CENTER #	65969410	FILING DATE	03/13/2012
CUSTOMER #	179511	FIRST NAMED INVENTOR	Gregory Porreca
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Thomas Meyers

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
MLB-002-01US-Response-061424.pdf		7	-	115 KB
MLB-002-01US-Response-061424-AMSB.pdf	(1-1)	1	Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)	70 KB
MLB-002-01US-Response-061424-CLM.pdf	(2-3)	2	Claims	52 KB
MLB-002-01US-Response-	(4-7)	4	Applicant Arguments/Remarks	87 KB

061424-REM.pdf		Made in an Amendment	
MLB-002_01US_rece.pdf	3	Request for Continued Examination (RCE)	1628 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
MLB-002-01US-Response-061424.pdf	A212F4D328BCC5ACC1A7CFC20A52442E339E1FF70B7A2801941E5BC38C96D2B408A79817BBA3C9F185C607069F89A9DE01412927BCA410DCAB3289BB5F2313B5
MLB-002-01US-Response-061424-AMSB.pdf	664B3A398C3C7592457B7E09DA311540D57A9F45BBC32B65DAF6A4DCC1718C6D15D07D4EC8A3759B56E541F98FC16E85C84FB90187D9943B4EDC378C4926E729
MLB-002-01US-Response-061424-CLM.pdf	D76A465E4D22337656D23F3137A7ACA60C538FFC243F156FDD9F116AFA4AE2B29F11B1F382940B602906D57AFE45D1F1A241E7F9EF5F6663D2AB279A9C23FF54
MLB-002-01US-Response-061424-REM.pdf	5C946FB71ACF620CBA2F9457D990FAE6F9D59D9F0B0FFD43C147C97B5833C7D44501957B4EEDF5CA4F42D9F0470C1D6D08FD55CA7EB71B22447F0E623697028E
MLB-002_01US_rece.pdf	322B0BB3B5B730293983D816CCE81062194DE4AD12B2B44A10F54E0E5DF78A745913ED9DFDE3CC8863DDED53FBC3346CCEBCEBD7873DA52CD61F3FCDF52A52AF

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 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.

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. 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	13266862	Filing Date	2010-04-30	Docket Number (if applicable)	1006120.0009	Art Unit	1634
First Named Inventor	Gregory PORRECA			Examiner Name	STEVEN 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 _____

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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Signature of Registered U.S. Patent Practitioner			
Signature	/Thomas C. Meyers/	Date (YYYY-MM-DD)	2024-06-14
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.

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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 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.

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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.

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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.

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Molecular Loop Biosciences, Inc.		
APPLICATION NO.:	13/266,862	ART UNIT:	1634
FILING DATE:	March 13, 2012	CONF. NO.:	6082
EXAMINER:	Steven Pohnert		
TITLE:	METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS		

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

FILED ELECTRONICALLY

RESPONSE AND REQUEST FOR CONTINUED EXAMINATION

This paper is in response to the final Office Action mailed February 15, 2024, from the United States Patent and Trademark Office.

Amendments to the claims begins on page 2.

Remarks begin on page 5.

Applicant petitions for a one-month extension of time to bring the response deadline to June 17, 2024 (June 15, 2024, being a Saturday).

A Request for Continued Examination (RCE) is submitted herewith.

Applicant submits the fees or the extension and the RCE and authorizes any required fee to be charged to Deposit Account No. 604011.

Petitioner Illumina, Inc., EX1002, p. 2151

Amendments to the Claims

Please amend the claims as follows.

1. (Currently Amended) A method for analyzing a target nucleic acid, the method comprising:

providing a sample comprising nucleic acid comprising a target region;

contacting the sample with a probe set to generate hybridized probes, the probe set comprising a plurality of different molecular inversion probes (MIPs) comprising different nucleotide sequences, each MIP comprising a 5' targeting arm, a central region, a unique differentiator tag sequence, and a 3' targeting arm, wherein the targeting arms of each MIP hybridize on either side of the target region in the nucleic acid, wherein each of the MIPs captures at least the target region, and, wherein some of the MIPs in the probe set also capture additional nucleic acids flanking the target region;

converting the hybridized probes into a plurality of closed circularized probes, each comprising a copy of the target region and some comprising the additional flanking nucleic acids;

isolating the plurality of circularized probes; and

analyzing the target region by sequencing the probes to obtain sequence reads; and collapsing sequence reads that share one target and one differentiator tag into a single read.

2. (Canceled)

3. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, non-overlapping with the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

4. (Previously Presented) The method of claim 1, wherein the sequences of the 5' targeting arm and the 3' targeting arm of each probe are, respectively, different than the sequences of the 5' targeting arm and the 3' targeting arm of each other probe.

Petitioner Illumina, Inc., EX1002, p. 2152

5-67. (Canceled)

68. (Previously Presented) The method of claim 1, wherein the 5' targeting arm and the 3' targeting arm of each MIP, when hybridized on either side of the target region, are separated by a plurality of nucleotides on the nucleic acid.

69. (Previously Presented) The method of claim 1, wherein the target region comprises at least 50 base pairs of DNA

70. (Previously Presented) The method of claim 1, wherein each target region is captured by at least three different MIPs.

71. (Previously Presented) The method of claim 70, wherein the step of analyzing the target region comprises sequencing the copy of the target and the additional flanking nucleic acids to generate sequence reads.

72. (Previously Presented) The method of claim 71, wherein the sequencing is next generation sequencing.

73. (Previously Presented) The method of claim 72, wherein the step of analyzing comprises averaging the nucleotide base-composition of the sequence reads from the at least three different MIPs.

74. (Previously Presented) The method of claim 1, wherein the plurality of MIPs include at least a first MIP that includes a primer-binding region that can be used to sequence the target region.

75-76. (Cancelled)

Petitioner Illumina, Inc., EX1002, p. 2153

Remarks

With entry of this amendment, claims 1, 3, 4, and 68-75 are pending, with claim 1 being the only independent claim. Claim 1 is amended. Support for the amendments may be found throughout the as-filed application including for example at least at page 90, lines 14-25.

No new matter is added.

Rejections under 35 U.S.C. §103

The Office Action on page 3 states that claims 1, 68, 70-71, and 75-76 are rejected under §103 over Daly, 2007, Clin Chem 53(7):1222-1230, Hardenbohl, 2005, Gen Res 15:269-275, Nilsson, 2006, Trends Biotech 24(2):83-88, US 2007/0212704 to Dong, Streit, 2003, Mol Genet Metab 78(4):259-264, Mockler, 2005, Genomics 85:1-15, Jares, 2006, Clin Trans Oncol 8(3):161-172, WO 95/11995 to Chee, and Johnson, 2005, Trends Gen 21:93-102. On pages 14-15, claims 1, 3-4, 68-71, and 74-76 are so rejected over Krishnakumar, 2008, PNAS 105:9296-9301, Nilsson, Dong, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, Johnson, Blasczyk, 1996, Tiss Antigens 47:102-110), and Kotsch, 1999, Tiss Antigens 53:486-497. On pages 22-23, claims 73-73 are so rejected over Krishnakumar, Nilsson, Streit, Daly, Hardenbohl, Mockler, Jares, Chee, Johnson, Blasczyk, Kotsch, and Chaisson, 2004, Bioinformatics 20:2067-2074.

The claims are not obvious.

A determination of obviousness requires basic factual inquiries into the scope and content of the prior art as well as the differences between the claimed invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). When a patent claim includes a limitation that is wholly missing from the prior art, then that prior art does not support a conclusion of obviousness. *Arendi S.A.R.L. v. Apple, Inc.*, 832 F.3d 1355, 1366-67 (Fed. Cir. 2016).

Independent claim 1 recites a method for analyzing a target nucleic acid. As recited, the method includes contacting a target region in a nucleic acid with a plurality of MIPs that each include a unique differentiator tag. The claim states that each of the plurality of MIPs captures at least the target region. Further, some of the MIPs also capture additional sequence flanking the target. The probes are circularized and isolated. Claim 1 then recites sequencing the probes to obtain sequence reads and collapsing sequence reads that share one target and one differentiator tag into a single read.

The asserted prior art, now matter how combined, does not teach or suggest the use o unique tag sequences in capture probes to de-duplicate sequence reads after sequencing. For at least that reason, the prior art that has been asserted does not support a conclusion of obviousness.

Daly only reports the use of MIPs to assay genetic variants in genes involved in drug metabolism. *Daly, Abstract*. Daly states that they apply the MIP technology cited in the Hardenbol reference. Id., 1223.

Hardenbol reports the use of MIP technology and four-color, single-array detection in genotyping 12,000 SNPs per reaction for studies of genetic association and linkage disequilibrium. *Hardenbol, Abstract.* For SNP detection, Hardenbol states that a probe with hybridizes to a target with abutting ends, which "leaves a single base gap at the location of the SNP". *Id., 270*. Hardenbol states each probe contains a unique tag sequence, which is only used for capture to an complementary tag array. Nilsson only reports also MIPs that can interrogate a single base. Nilsson reviews technologies that use specific DNA circularization coupled to DNA amplification and states that padlock probes and MIPs provide parallel, high throughput single nucleotide polymorphism (SNP) genotyping. *Nilsson, Abstract*. Nilsson states that the MIP assay has been applied to a 12,000 SNP multiplex genotyping project, citing the Hardenbol reference. *Id., 84*. Nilsson—like the other references—says nothing of using a unique tag sequence to "collapse" (or deduplicate) sequence reads. Krishnakumar reports using long padlock probes (LPPs) (probes >300 bases in size) to amplify and analyze sequences of up to 50 bases in length, in parallel. *Krishnakumar, Abstract*. Krishnakumar reports that, as long as one excludes exons for which primers would require a BsaI or an MlyI site, the LPPs are useful for the simultaneous multiplex amplification of DNA sequences in a single tube for targets that can range from <100 to 500 bp. *Id., 9298, 9299*.

Dong, Streit, Mockler, Jares, Chee, Johnson, Blasczyk, Kotsch, and Chaisson do not mention MIPs and do not cure the deficiencies of Daly, Hardenbol, Nilsson and Krishnakumar.

Dong only reports methods for amplifying target nucleic acids while reducing non-specific fluorescence and undesired amplification products, using enzyme inhibitors that comprise a nucleotide sequence and at least one quencher. *Dong, Abstract*. Dong states that amplification may include padlock versions of ligase-mediated amplification. *Id., [0109]*. Streit reports mutation detection in the CFTR gene. *Streit at Abstract and 261, Table 2.* Streit simply

reports amplifying regions of the CFTR gene. *Id. at 260*. Mockler is a review article on microarray tiling experiments. *Mockler Abstract.* Jares, like Mockler, is also a review article comparing microarray tiling experiments of gene expression and DNA copy number. *Jares. Abstract.* Chee only reports chips of immobilized probes useful for comparing a reference polynucleotide sequence of known sequence with an, e.g., mutant target sequence. *WO 95/11995, Abstract*. Johnson, like Mockler and Jares, reports microarray tiling experiments of gene expression. *Johnson, Abstract.* The probes in Johnson are oligonucleotides designed against a known or predicted reference genome. *Id., at 93.* The probes do not have any unique tag used to deduplicate sequence reads. Blasczyk reports only the improvements to PCR products to overcome the limitations of Sanger sequencing. *Blasczyk, 102-103.* Blasczyk reports the use of two additional primers to capture the 5' and 3' ends of a target nucleic acid, typically lost during Sanger sequencing. Kotsch (like Blasczyk) seeks to overcome drawbacks in PCR strategies that "that do not allow sequence analysis of the 5' and 3' ends of the 2nd exon" in HLA-DRB genes. *Kotsch, 487.* Kotch reports the use of three nested primers that correspond to three variants of a conserved region in the 3' end of intron 1 of the HLA-DRB gene. *Id., 488*. Chaisson reports only that new computer-assisting assemblies may facilitate assembling short reads together, for example from pyrosequencing reads. *Chaisson, 2067-68.*

Factual analysis reveals that the prior art does not teach or suggest MIP capture of an unknown target sequence using MIPs that contain unique differentiator tags in which, after sequencing, like sequence reads are collapsed into a single read.

Because that element of independent claim 1 cannot be found among any of the prior art that the Office has asserted, claim 1 is not obvious.

Because the only independent claim is not obvious, none of the claims are obvious.

The rejections under §103 should be withdrawn.

Petitioner Illumina, Inc., EX1002, p. 2156

Conclusion

Applicant submits that all rejections have been addressed and overcome. Applicant requests a Notice of Allowance.

Dated June 14, 2024

Respectfully submitted,
WITHERS BERGMAN LLP

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Petitioner Illumina, Inc., EX1002, p. 2157

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
13/266,862	06/14/2024 11:04:51 AM Z ET	MLB-002/01US 1006120/9

Title of Invention

METHODS AND COMPOSITIONS FOR EVALUATING GENETIC MARKERS

Application Information

APPLICATION TYPE	Utility - U.S. National Stage under 35 USC 371	PATENT #	-
CONFIRMATION #	6062	FILED BY	Kristina Scandore
PATENT CENTER #	65969410	AUTHORIZED BY	Thomas Meyers
CUSTOMER #	179511	FILING DATE	03/13/2012
INTL. APPLICATION #	-	INTL. FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Gregory Porreca

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 604011	E20246DB05395111	Kristina Scandore

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	800.00	1	800.00
2251	EXTENSION FOR RESPONSE WITHIN FIRST MONTH	88.00	1	88.00
			TOTAL AMOUNT:	$888.00

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

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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 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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/266,862

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	190		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	60		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	39 minus 20 =	* 19	x 30 =	570	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 125 =	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).			155			
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	1100		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 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/03/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 49	Minus	** 39	= 10	X $31 =	310	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $125 =	0	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	310	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/BRENDA 13522338 HINES/

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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 13/266,862	Filing Date 03/13/2012	☐ 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 01/29/2015

	(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))	* 39	Minus	** 49	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	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
/DANTE SMITH/

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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)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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	**190**
☐ 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	**190**

APPLICATION AS AMENDED – PART II

AMENDMENT **09/09/2013**

	(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))	* 39	Minus	** 49	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	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
/GLORIA TRAMMELL/

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

(Column 1) (Column 2)

FOR	NUMBER FILED	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

(Column 1) (Column 2) (Column 3)

AMENDMENT	04/08/2013	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 39	Minus	** 49	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 3	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**

(Column 1) (Column 2) (Column 3)

AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	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
/ANNIE SINGLETON/

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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 **04/21/2016**

	(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))	* 39	Minus	** 49	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	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
/KIM DOWNING/

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☒ 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 **05/09/2018**

	(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))	* 38	Minus	** 49	= 0	X $50 =	0
Independent (37 CFR 1.16(h))	* 3	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
ANGELA JOHNSON

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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	09/18/2017	(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))	* 38	Minus	** 49	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 3	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
STELLA LITTLE

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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 10/10/2016

	(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))	* 37	Minus	** 49	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	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
GLORIA ANTHONY

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PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 125 =	
☐ 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	04/21/2020							
	Total (37 CFR 1.16(i))	* 5	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".	/WILLIAM N PHILLIPS/
*** 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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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 125 =	
☐ 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	05/14/2019							
	Total (37 CFR 1.16(i))	* 4	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.	

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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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☑ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 125 =	
☐ 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	01/09/2019	(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))	* 3	Minus	** 49	= 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".	/ANGELA D JOHNSON/
*** 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 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
13/266,862	03/13/2012	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			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 $250 ($125 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			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	10/28/2011	(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 ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 39	Minus	** 39	= 0	X $30 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $125 =	0	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	0	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	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 number found in the appropriate box in column 1.

Legal Instrument Examiner:
/BARBARA FRIESON/

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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 09/14/2015	(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))	* 39	Minus	** 49	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	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
/KIM DOWNING/

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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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/266,862

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	190		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	60		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	125		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	39 minus 20 =	* 19	x 30 =	570	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 125 =	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).			155			
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	1100		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.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $125 =	
☐ 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	07/27/2021	(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))	* 9	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 1	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

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.	

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.

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 125 =	
☐ 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	12/06/2023	(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	= 0		x $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $ 192 =	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".	/JACQUELYN L WILLIAMS/
*** 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)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/266,862	Filing Date 03/13/2012	☐ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 125 =	
☐ 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	04/24/2023	(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))	* 12	Minus	** 49	= 0		x $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $ 192 =	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".	/LINDA HUMES/
*** 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 13/266,862	Filing Date 03/13/2012	☐ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 125 =	
☐ 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	10/17/2022	(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))	* 9	Minus	** 20	= 0		x $ 50 =	0
	Independent (37 CFR 1.16(h))	* 1	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

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".	/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 13/266,862	Filing Date 03/13/2012	☐ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 125 =	
☐ 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	12/27/2021	(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))	* 9	Minus	** 20	= 0		x $ 50 =	0
	Independent (37 CFR 1.16(h))	* 1	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

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".	/MARISSA R BLYTHER/
*** 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 13/266,862	Filing Date 03/13/2012	☐ 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 $30 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 125 =	
☐ 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	10/08/2020	(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))	* 5	Minus	** 20	= 0		x $ 50 =	0
	Independent (37 CFR 1.16(h))	* 1	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

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".	/MARISSA R BLYTHER/
*** 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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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
13266862	

Applicant(s) Gregory Porreca

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1		1			
2		1		1		
3		1		1		
4		1		1		
5	1		---	---		
6		2	---	---		
7		2	---	---		
8		2	---	---		
9	1		---	---		
10		1	---	---		
11	1		---	---		
12	1		1			
13		1		1		
14		2		1		
15		(1)		1		
16		(1)		1		
17	1		---	---		
18		1	---	---		
19		(1)	---	---		
20	1		1			
21		1		1		
22		2		1		
23		2		1		
24		2		1		
25		2		1		
26		2		1		
27		2		1		
28	1			1		
29		1		1		
30		1		1		
31		1	---	---		
32		1	---	---		
33		3		1		
34		(1)	---	---		
35		(1)	---	---		
36		(1)		1		
37		(1)		1		
38		(1)		1		
39		(1)	---	---		
40		(1)		1		
41		(1)		1		
42		(1)		1		
43		(1)		1		
44		(1)		1		
45		(1)		1		
46		(1)		1		
47		(1)		1		
48		(1)	---	---		
49		(1)	---	---		
50		(1)		1		
Total Indep	13		3		0	
Total Depend	66	↵	36	↵	0	↵
Total Claims	79		39		0	

CLAIMS	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
51		(1)		1		
52		(1)		1		
53		(1)		1		
54		(1)		1		
55		(1)		1		
56		(1)		1		
57	1		---	---		
58	1		---	---		
59		1	---	---		
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61		1	---	---		
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64		2	---	---		
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