Attorney Docket No.: 81503-AAA/GJG/ADR

Prior Application Information

Serial No.: 15/063,278

Class 435 Subclass 006.110

Examiner: Frank Wei Min Lu

Group Art Unit: 1634

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

Date: February 7, 2019

Sir:
This is a request for filing a X continuation _____ divisional _____ continuation-in-part application under 37 CFR § 1.53(b) of pending application U.S. Serial No. 15/063,278 filed on March 7, 2016 of

James Hicks, Nicholas Navin, Jennifer Troge, Zihua Wang, and Michael Wigler

for

Inventor(s)

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Title of Invention
including the following:

X a copy of the prior application (106 pages in total), including 70 pages of specification; 17 page(s) of claims; 1 page(s) of abstract; 3 page(s) of sequence listing; and 15 sheet(s) of drawings)

X Oath or Declaration of Applicant(s) (X signed copy from parent; _____ signed new; _____ unsigned)

_____ Power of Attorney (_____ signed copy from parent; _____ signed new; _____ unsigned)

X Preliminary Amendment (15 pages)

_____ Amend the specification by inserting before the first line the sentence: --This application is a ___ continuation ___divisional ___continuation-in-part of U.S. Serial No. _____, filed _____, the contents of which are hereby incorporated by reference.--

_____ A verified statement to establish small entity status under 37 C.F.R. § 1.27:

_____ is enclosed.

_____ was filed in the prior application and such status is still proper and desired.

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_____ The prior application is assigned of record to:_____, and a copy of the assignment is enclosed.

_____ Information Disclosure Statement, including Form PTO-1449 (Copies of citations are included: Yes_____; No_____)

_____ Non-Publication Request, if prior application also had such request (Form PTO/SB/135 must be attached)

__X__ Computer Readable Form (CRF) of Sequence Listing and Statement Verifying Identity of CRF and Sequence Listing - OR - Request pursuant to 37 CFR § 1.821(e) to use the CRF Sequence Listing from the parent.

_____ Applicant(s) hereby claim(s) priority based upon the following foreign application(s) under 35 U.S.C. §119

Country	Application No.	Filing Date

_____ Certified copy of previously filed foreign application(s) enclosed

_____ Certified copy of previously filed foreign application(s) filed in prior application U.S. Serial No._____, filed on _____.

The filing fee is calculated as follows:

NUMBER OF CLAIMS AS FILED, MINUS ALL CLAIMS CANCELED BY ANY ACCOMPANYING PRELIMINARY AMENDMENT

	Number Filed		Number Extra*				Rate: Small Entity	Rate: Other Entity		Fee: Small Entity	Fee: Other Entity
Total Claims	20	-20 =	0	X			$ 50	$ 100	=	$ 0	$
Independent Claims	1	-3 =	0	X			$ 230	$ 460	=	$ 0	$
Total Number Of Pages	118 X 0.75 = 91	-100 =	0	÷ by 50	0†	X	$ 200	$ 400	=	$ 0	$
Multiple Dependent Claims Present: ___Yes _X_No							$ 410	$ 820	=	$	$
Non-English Specification: ___ Yes _X_ No							$ 70	$ 140	=	$	$
Basic Filing Fee							$ 150	$ 300	=	$ 75	$
Basic Filing Fee For E-Filing For Small Entity							$ 75		=		
Search Fee									=	$330	$680
Examination Fee									=	$380	$760
Total Fee										$785	$

* If less than zero, enter "0"

† Round upwards to integer, e.g.. 1.1 = 2, and insert

_____ A check in the amount of $_____ is enclosed.

__X__ The Commissioner is hereby authorized to charge any additional fees required or credit any overpayment to Deposit Account No. 03-3125 as follows:

_____ Filing fees under 37 CFR § 1.16
_____ Patent application processing fees under 37 CFR § 1.17
_____ Prioritized Examination fee in the amount of $4,000.00
_____ Processing fee in the amount of $140.00
__X__ Fee for Filing a Petition Under 37 CFR § 1.84(a)(2) to accept Color Drawings in the amount of $70.00.

__X__ Please charge Deposit Account No. 03-3125 in the amount of $855.00.

_____ Two copies of this Patent Application Transmittal Letter

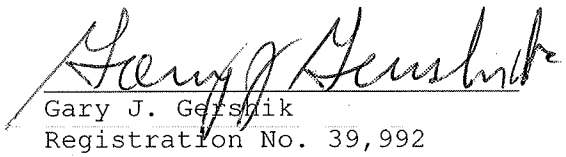
_____ Return Receipt Postcard

_____ Express Mail Certificate of Mailing Label No._____dated _____

__X__ Other (identify): Application Data Sheet 37 CFR § 1.76
Request for Prioritized Examination Under 37 C.F.R. 1.102(e)

Petition Under 37 CFR § 1.84(a)(2) to accept Color Drawings

Respectfully submitted,



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Registration No. 39,992
Attorneys for Applicants
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New York, New York 10112
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Sequence Listing

Please replace the Sequence Listing filed in the parent application with the Substitute Sequence Listing filed with the subject application herewith as a text file named "190207_81503_AAA_Sequence_Listing_ADR.txt".

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REMARKS

In this Amendment, applicants have canceled claims 2-67. Accordingly, upon entry of this Amendment, claim 1 is pending and under consideration in the subject application.

Sequence Listing

Applicants attach hereto as **Exhibit A** a Statement of Compliance under 37 C.F.R. § 1.825(a) certifying that the Sequence Listing submitted herewith as a text file does not introduce any new matter into the subject application. The Sequence Listing lists the correct file reference and prior application data for the subject application.

In accordance with the guidance set forth in section I1 of "Legal Framework for EFS-Web (06April11)" published by the U.S. Patent and Trademark Office at www.uspto.gov/patents/process/file/efs/guidance/New_legal_framework.jsp, applicants are not submitting herewith a statement under 37 C.F.R. § 1.821(f), since the text file submitted herewith will serve as both the "paper copy" and the "computer readable form" of the Sequence Listing.

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AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Original) A method for obtaining from genomic material genomic copy number information unaffected by amplification distortion, comprising:

a) obtaining segments of the genomic material;

b) tagging the segments with substantially unique tags to generate tagged nucleic acid molecules, such that each tagged nucleic acid molecule comprises one segment of the genomic material from step (a) and a tag;

c) subjecting the tagged nucleic acid molecules to amplification by polymerase chain reaction (PCR);

d) generating tag associated sequence reads by sequencing the product of step (c);

e) assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding to a segment of the genomic material to a location on the genome; and

f) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the genome,

thereby obtaining genomic copy number information unaffected by amplification distortion.

2.-67. (Cancelled).

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	81503-AAA/GJG/ADR
	Application Number	
Title of Invention	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	James		Hicks	

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

City	State/Province	Country of Residence
Locust Valley	NY	US

Mailing Address of Inventor:

Address 1	3 Great Meadows Road
Address 2	
City	Locust Valley
State/Province	NY
Postal Code	11560
Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Nicholas		Navin	

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

City	State/Province	Country of Residence
Houston	TX	US

Mailing Address of Inventor:

Address 1	1621 Wichita Street
Address 2	
City	Houston
State/Province	TX
Postal Code	77004
Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jennifer		Troge	

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	81503-AAA/GJG/ADR
	Application Number	
Title of Invention	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION	

City	Oyster Bay	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	100 Simcoe Street		
Address 2			
City	Oyster Bay	State/Province	NY
Postal Code	11771	Country	US

Inventor 4 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Zihua		Wang	

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

City	Huntington	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	13 Meadowlawn Street		
Address 2			
City	Huntington	State/Province	NY
Postal Code	11743	Country	US

Inventor 5 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Michael		Wigler	

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

City	Cold Spring Harbor	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	52 Snake Hill Road		
Address 2			
City	Cold Spring Harbor	State/Province	NY
Postal Code	11724	Country	US

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

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

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

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	Application Number	
Title of Invention	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION	

Customer Number	23432		
Email Address	patentdocketing@cooperdunham.com	Add Email	Remove Email

Application Information:

Title of the Invention	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		
Attorney Docket Number	81503-AAA/GJG/ADR	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	11	**Suggested Figure for Publication (if any)**	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	23432		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	81503-AAA/GJG/ADR
	Application Number	
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Domestic Benefit/National Stage Information:

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

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15/063278	2016-03-07
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/063278	Continuation of	13/278333	2011-10-21	9404145	2013-08-02

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13/278333	Claims benefit of provisional	61/510579	2011-07-22
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13/278333	Claims benefit of provisional	61/406067	2010-10-22

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

Foreign Priority Information:

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

Remove

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

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	81503-AAA/GJG/ADR
	Application Number	
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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	81503-AAA/GJG/ADR
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Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

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Title of Invention	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION	

Applicant Information:

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

Applicant 1 — Remove

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Cold Spring Harbor Laboratory		
Mailing Address Information For Applicant:			
Address 1	One Bungtown Road		
Address 2			
City	Cold Spring Harbor	**State/Province**	NY
Country	US	Postal Code	11724
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

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Assignee 1

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

Remove

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

Organization Name	Cold Spring Harbor Laboratory

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	One Bungtown Road		
Address 2			
City	Cold Spring Harbor	**State/Province**	NY
Country i	US	Postal Code	11724
Phone Number		Fax Number	
Email Address			

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

Signature:

Remove

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

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

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

Signature	/Gary J. Gershik/			Date (YYYY-MM-DD)	2019-02-07
First Name	Gary	Last Name	Gershik	Registration Number	39992

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

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	James Hicks et al.
U.S. Serial No.	:	Not Yet Known (continuation of U.S. Serial No. 15/063,278, filed March 7, 2016)
Filing Date	:	Herewith
Confirmation No.	:	Not Yet Known
For	:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

30 Rockefeller Plaza
20th Floor
New York, New York 10112
February 7, 2019

BY EFS
Commissioner for Patents
Alexandria, VA

PRELIMINARY AMENDMENT AND PETITION UNDER 37 C.F.R. § 1.84(a)(2) TO ACCEPT COLOR DRAWINGS FILED

This Preliminary Amendment is submitted in connection with the above-identified continuation application filed herewith.

Further the accompanying Petition is submitted under 37 C.F.R. § 1.84(a)(2) to accept color drawings filed with the subject application.

A **Sequence Listing** is referenced on page **2** of this paper.

Amendments to the Claims begin on page **3** of this paper.

Remarks begin on page **4** of this paper.

A **Statement of Compliance under 37 C.F.R. § 1.825(a)** is referred to on page **4** of this paper and submitted herewith as **Exhibit A.**

A **Petition Under 37 C.F.R. § 1.84(a)(2) to Accept Color Drawings Filed** begins on page **5.**

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Varietal Counting of Nucleic Acids for Obtaining Genomic Copy Number Information
First Named Inventor/Applicant Name:	James Hicks
Filer:	Gary J. Gershik/Darren Haber
Attorney Docket Number:	81503-AAA/GJG/ADR

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	75	75
UTILITY SEARCH FEE	2111	1	330	330
UTILITY EXAMINATION FEE	2311	1	380	380
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
PETITION FEE-37CFR 1.17(H) (GROUP II)	2464	1	70	70

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**855**

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

This application is a continuation of U.S. Serial No. 15/063,278, filed March 7, 2016, a continuation of U.S. Serial No. 13/278,333, filed October 21, 2011, now U.S. Patent No. 9,404,156, issued August 2, 2013, which claims the benefit of U.S. Provisional Application Nos. 61/510,579, filed July 22, 2011, and 61/406,067, filed October 22, 2010 the contents of each of which are hereby incorporated by reference in their entirety into this application.

This invention was made with government support under grant W81XWH-09-1-0591. The Government has certain rights in the invention.

Throughout this application, various publications are referenced by numbers in parentheses. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

Reference to a Sequence Listing

This application incorporates-by-reference nucleotide and/or amino acid sequences which are present in the file named "190207_81503_AAA_Sequence_Listing_ADR.txt" which is 2.59 kilobytes in size, and which was created February 7, 2019 in the IBM-PC machine format, having an operating system compatibility with MS-Windows, which is contained in the text file filed February 7, 2019 as part of this application.

Background of the Invention

Genomic copy number information is commonly obtained using whole genome amplification (WGA). The endemic problem with the WGA method is over-sampling of certain regions, yielding a non-uniform amplification of the genome (1). WGA methods begin with the step that initiates the process, a polymerase (Phi 29) makes a strand from genomic DNA utilizing a random primer coupled to an adaptor for subsequent PCR (Figure 1). If the input DNA strands are referred to as the "0-th derivative", and the first synthesized strand as a "first derivative," subsequent strands are called the (n+1)-th derivative if their template was an n-th derivative. Only strands that are 2-nd derivative or higher become amplified in the PCR step, resulting in a 'stacking' over the regions 'chosen' by the polymerase for the first derivative.

Coverage of the genome by sequencing WGA of single cell DNA is limited by the stacking phenomenon (Figure 2). Thus it is difficult to obtain single cell measurements, particularly when based on WGA, due to distortions that originate from stochastic sampling and amplification steps. Moreover, the current method of WGA is a black box, with the unspecified reagents purchased from a vendor, which hampers optimization. Moreover, the WGA method does not extend to a method usable for single cell RNA profiling.

Ligation-mediated PCR was developed in an attempt to solve the above-identified problems inherent in WGA. In this method, adaptors are ligated to an *MseI* restriction endonuclease digest of genomic DNA from a single cell, followed by PCR amplification using primers complementary to the adaptors. The amplified DNA is then used for CGH or DNA sequencing (2,3). However, like WGA, the method still requires an amplification step.

Parameswaran et al. (2007) and U.S. Patent No. 7,622,281 describe methods of labeling nucleic acid molecules with

barcodes for the purpose of identifying the source of the nucleic acid molecules, thereby allowing for high-throughput sequencing of multiple samples (4,5). Eid et al. (2009) describe a single molecule sequencing method wherein single-molecule real time sequencing data is obtained from a DNA polymerase performing uninterrupted template-directed synthesis using four distinguishable fluorescently labeled dNTPs (6). However, these methods do not provide genomic information unaffected by amplification distortion.

Miner et al. (2004) describe a method of molecular barcoding to label template DNA prior to PCR amplification, and report that the method allows for the identification of contaminant and redundant sequences by counting only distinctly tagged sequences (22). U.S. Patent No. 7,537,897 describes methods for molecular counting by labeling molecules of an input sample with unique oligonucleotide tags and subsequently amplifying and counting the number of different tags (23). Miner et al. and U.S. Patent No. 7,537,897 both describe labeling of input nucleic acid molecules by ligation, which has been found to be an inefficient reaction.

McCloskey et al. (2007) describe a method of molecular encoding which does not use ligation but instead uses template specific primers to barcode template DNA molecules prior to PCR amplification (24). However, such a method requires that template specific primers be made for each species of template DNA molecule studied.

As described herein, obtaining accurate genomic copy number information by high-throughput sequencing of genomic DNA prepared by WGA methods is hampered by the copy number distortions introduced by non-uniform amplification of genomic DNA. Thus, there exists a need for a method that allows for copy number determination free of distortions caused by amplification steps and which allows for accurate and efficient

copy number determination of complex samples. Such a method should also be robust using existing methodologies for high volume, massively parallel sequencing.

SUMMARY OF THE INVENTION

A method is provided for obtaining from genomic material genomic copy number information unaffected by amplification distortion, comprising:

a) obtaining segments of the genomic material;

b) tagging the segments with substantially unique tags to generate tagged nucleic acid molecules, such that each tagged nucleic acid molecule comprises one segment of the genomic material from step (a) and a tag;

c) subjecting the tagged nucleic acid molecules to amplification by polymerase chain reaction (PCR);

d) generating tag associated sequence reads by sequencing the product of step (c);

e) assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding to a segment of the genomic material to a location on the genome; and

f) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the genome,

thereby obtaining genomic copy number information unaffected by amplification distortion.

Also provided is a method for obtaining from mRNA transcripts mRNA copy number information unaffected by amplification distortion, comprising:

a) obtaining cDNA from the mRNA transcripts;

b) optionally obtaining segments of the cDNA;

c) tagging the cDNA or segments of cDNA with substantially unique tags to generate tagged nucleic acid molecules, such that each tagged nucleic acid molecule comprises

i) one cDNA from step (a) or one segment of the cDNA from step (b), and

ii) a tag;

d) subjecting the tagged nucleic acid molecules to amplification by polymerase chain reaction (PCR);

e) generating tag associated sequence reads by sequencing the product of step (d);

f) assigning each tagged nucleic acid molecule to a location on a cDNA library associated with the mRNA transcripts by mapping the subsequence of each tag associated sequence read corresponding to a cDNA or a segment of cDNA to a location on the cDNA library; and

g) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the cDNA library,

thereby obtaining mRNA copy number information unaffected by amplification distortion.

Also provided is a method for obtaining from mRNA transcripts mRNA copy number information unaffected by amplification distortion, comprising:

a) generating tagged nucleic acid molecules, comprising:

i) subjecting the mRNA transcripts to a polymerase reaction in the presence of primers capable of hybridizing to the polyA tail of the mRNA transcripts under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

ii) adding a polynucleotide tail to the first order derivative strands; and

iii) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (ii) under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (i) and (iii) comprise substantially unique primers, thereby generating tagged nucleic acid molecules;

b) subjecting the tagged nucleic acid molecules to polymerase chain reaction (PCR) amplification;

c) generating tag associated sequence reads by sequencing the product of step (b);

d) assigning each tagged nucleic acid molecule to a location on a cDNA library associated with the mRNA transcripts by mapping the subsequence of each tag associated sequence read corresponding to a mRNA transcript to a location on the cDNA library; and

e) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the cDNA library,

thereby obtaining mRNA copy number information unaffected by amplification distortion.

Also provided is a method for obtaining from genomic material DNA methylation information unaffected by amplification distortion, comprising:

a) obtaining segments of the genomic material;

b) adding a polynucleotide tail to the ends of the segments of the genomic material to generate zero-th order derivative strands;

c) subjecting the zero-th order derivative strands to a polymerase reaction in the presence essentially unique primers, wherein the essentially unique primers are capable of hybridizing to the polynucleotide tail of the zero-th order strands, under conditions that promote the formation of only one complement, thereby generating tagged nucleic acid molecules;

d) separating the tagged nucleic acid molecules into a group consisting of hemi-methylated

tagged nucleic acid molecules and a group consisting of unmethylated tagged nucleic acid molecules;

e) subjecting each group of step (d) to amplification by polymerase chain reaction (PCR);

f) generating tag associated sequence reads by sequencing the product of step (e);

g) assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding to a segment of the genomic material to a location on the genome; and

h) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the genome,

thereby obtaining DNA methylation information unaffected by amplification distortion.

Also provided is a composition of matter derived from genomic material comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining segments of the genomic material;

b) adding a polynucleotide tail to the ends of the segments of the genomic material to generate zero-th order derivative strands;

c) subjecting the zero-th order derivative strands of step (b) to a polymerase reaction in the presence of primers capable of

hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

d) adding a polynucleotide tail to the first order derivative strands;

e) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the first order derivative strands under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (c) and (e) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

Also provided is a composition of matter derived from genomic material comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining segments of genomic material;

b) adding a polynucleotide tail to the ends of the segments of genomic material to generate zero-th order derivative strands,

c) subjecting the zero-th order derivative strands of step (b) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (b) under

conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

d) subjecting the product of step (c) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (b) under conditions which promote the formation of only one complement, wherein the primers of step (d) have different nucleotide sequences than the primers of step (c), and wherein the polymerase has 3′-5′ proofreading activity,

wherein the primers of at least one of steps (c) and (d) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

Also provided is a composition of matter derived from a mRNA transcripts comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining cDNA from the mRNA transcripts;

b) optionally obtaining segments of the cDNA; and

c) tagging the cDNA or segments of cDNA with substantially unique tags to generate tagged nucleic acid molecules, wherein each tagged nucleic acid molecule comprises

i) one cDNA from step (a) or one segment of the cDNA from step (b) and

ii) a tag.

Also provided is a composition of matter derived from mRNA transcripts comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining mRNA transcripts;

b) subjecting the mRNA transcripts to a polymerase reaction in the presence of primers capable of hybridizing to the polyA tail of the mRNA transcripts under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

c) adding a polynucleotide tail to the first order derivative strands;

d) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (c) under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (b) and d) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

Also provided is a kit for determining nucleic acid copy number information unaffected by amplification distortion comprising:

a) a terminal transferase, and

b) plurality of substantially unique primers,

wherein the substantially unique primers comprise substantially unique tags, and wherein the substantially unique primers are capable of hybridizing to the polynucleotide tail of a nucleic acid molecule which has a polynucleotide tail added by the terminal transferase.

BRIEF DESCRIPTION OF THE FIGURES

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Figure 1. Whole Genome Amplification (WGA).

Figure 2. Genome coverage comparison.

Genomic coverage comparison of 7 sequencing lanes from one single cell library versus 7 lanes from a million cell library. Stacking causes the single cell reads to be concentrated over the first derivative reads from WGA. More reads yield diminishing returns.

Figure 3. Sequencing read counts for CpG dinucleotides within selected CpG islands

Normal cell line SKN-1 (A,C,E) and breast cancer line MDA-MB-231 (B,D,F). Orange indicates T residues (unmethylated). Blue indicates C residues (methylated). Counts of the plus strand are above the X-axis, and counts on the minus strand are below.

Figure 4. Comparison of array CGH with 'sequence counting' for analyzing copy number data.

Graph shows a portion of chromosome 17 from FFPE sample JZ33 including raw (gray) ratio and segmented (green) data from array CGH, and raw sequence count data (orange) and its segmentation (blue).

Figure 5. ROMA CGH of sKBR3 compared with profiles of 3 independent single cell isolates derived from sparse DNA sequencing. (A) Batch DNA. (B, C, D) Single Cell.

Figure 6. Sequencing across the breakpoints of a homozygous deletion in cell on chromosome 5 line T47D.

Figure 7(A-C). Flowchart for genomic profiling by representational sequence counting

Figure 8. Scheme for varietal counting. Varietal tags are shown as random nucleotide sequences (N_{10})

Flowchart of one embodiment of the invention.

Figure 9(A and B). Nick ligation protocol

The sequence of primer A includes universal primer A (PrA; green), varietal tag (B; yellow), and oligo dT+CATG, the sequence of primer B includes universal primer B (PrB; orange) and oligo dT+CATG, PrA and PrB are universal primers, and cPrA(blue), cPrB (magenta), and cB(blue) are complementary to PrA, PrB and B, respectively.

Figure 10(A and B). Schema for targeted sequencing of regional markers

UfBPrA is forward primer, B (yellow) is tag, UrPrR is reverse primer, PrB (brown) is gene-specific reverse primer, Uf (orange) is universal forward primer, PrA (blue) is gene specific forward primer, Ur (magenta) is universal reverse primer.

Figure 11. Comparison of Varietal Counting with Sequence Counting

Figure 11A shows genome wide copy number data. Figure 11B shows partial genome copy number data.

DETAILED DESCRIPTION OF THE INVENTION

A method is provided for obtaining from genomic material genomic copy number information unaffected by amplification distortion, comprising:

a) obtaining segments of the genomic material;

b) tagging the segments with substantially unique tags to generate tagged nucleic acid molecules, such that each tagged nucleic acid molecule comprises one segment of the genomic material from step (a) and a tag;

c) subjecting the tagged nucleic acid molecules to amplification by polymerase chain reaction (PCR);

d) generating tag associated sequence reads by sequencing the product of step (c);

e) assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding to a segment of the genomic material to a location on the genome; and

f) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the genome,

thereby obtaining genomic copy number information unaffected by amplification distortion.

In an embodiment, the method further comprises estimating a genomic copy number of a region of the genome comprising more than one location on the genome by assigning as the copy

number of the region the highest count obtained in step (f) for the locations within the region.

In an embodiment, the method further comprises comparing a count obtained in step (f) for a location on the genome to a count for the same location obtained from a reference sample, thereby estimating a relative genomic copy number of the location.

In an embodiment, the method further comprises

a) summing the counts obtained in step (f) for locations on the genome which comprise a first region of the genome, wherein the first region comprises more than one location;

b) summing the counts obtained in step (f) for locations on the genome which comprise a second region of the genome, wherein the second region is comprised of a number of locations which is comparable to the number of locations of the first region;

c) comparing the value obtained in step (a) to the value obtained in step (b),

thereby estimating the relative genomic copy number of the first region of the genome to the genomic copy number of the second region of the genome.

Step (b) of the above embodiment may further comprise

i) summing the counts obtained in step (f) for locations on the genome which comprise a third region of the genome, wherein the third region is comprised of a number of locations which is comparable to the

number of locations of the first region; and

ii) obtaining an average of the sum of the counts obtained in step (f) for locations which comprise the second region and the sum of the counts obtained in step (f) for locations which comprise the third region.

In an embodiment of the method, the second region of the genome comprises a centromere.

In an embodiment, the method further comprises summing the counts obtained in step (f) for locations which comprise a region of the genome, and comparing the sum to a sum obtained from a reference sample for the same region of the genome, thereby estimating a relative genomic copy number of the region of the genome.

Also provided is a method for obtaining from mRNA transcripts mRNA copy number information unaffected by amplification distortion, comprising:

a) obtaining cDNA from the mRNA transcripts;

b) optionally obtaining segments of the cDNA;

c) tagging the cDNA or segments of cDNA with substantially unique tags to generate tagged nucleic acid molecules, such that each tagged nucleic acid molecule comprises

i) one cDNA from step (a) or one segment of the cDNA from step (b), and

ii) a tag;

d) subjecting the tagged nucleic acid molecules to amplification by polymerase chain reaction (PCR);

e) generating tag associated sequence reads by sequencing the product of step (d);

f) assigning each tagged nucleic acid molecule to a location on a cDNA library associated with the mRNA transcripts by mapping the subsequence of each tag associated sequence read corresponding to a cDNA or a segment of cDNA to a location on the cDNA library; and

g) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the cDNA library,

thereby obtaining mRNA copy number information unaffected by amplification distortion.

Also provided is a method for obtaining from mRNA transcripts mRNA copy number information unaffected by amplification distortion, comprising:

a) generating tagged nucleic acid molecules, comprising:

i) subjecting the mRNA transcripts to a polymerase reaction in the presence of primers capable of hybridizing to the polyA tail of the mRNA transcripts under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

ii) adding a polynucleotide tail to the first order derivative strands; and

iii) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (ii) under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (i) and (iii) comprise substantially unique primers, thereby generating tagged nucleic acid molecules;

a) subjecting the tagged nucleic acid molecules to polymerase chain reaction (PCR) amplification;

b) generating tag associated sequence reads by sequencing the product of step (b);

c) assigning each tagged nucleic acid molecule to a location on a cDNA library associated with the mRNA transcripts by mapping the subsequence of each tag associated sequence read corresponding to a mRNA transcript to a location on the cDNA library; and

d) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the cDNA library,

thereby obtaining mRNA copy number information unaffected by amplification distortion.

Also provided is a method for obtaining from genomic material DNA methylation information unaffected by amplification distortion, comprising:

a) obtaining segments of the genomic material;

b) adding a polynucleotide tail to the ends of the segments of the genomic material to generate zero-th order derivative strands;

c) subjecting the zero-th order derivative strands to a polymerase reaction in the presence essentially unique primers, wherein the essentially unique primers are capable of hybridizing to the polynucleotide tail of the zero-th order strands, under conditions that promote the formation of only one complement, thereby generating tagged nucleic acid molecules;

d) separating the tagged nucleic acid molecules into a group consisting of hemi-methylated tagged nucleic acid molecules and a group consisting of unmethylated tagged nucleic acid molecules;

e) subjecting each group of step (d) to amplification by polymerase chain reaction (PCR);

f) generating tag associated sequence reads by sequencing the product of step (e);

g) assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding

to a segment of the genomic material to a location on the genome; and

h) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the genome,

thereby obtaining DNA methylation information unaffected by amplification distortion.

In an embodiment of the methods, tagging the segments to generate tagged nucleic acid molecules comprises:

a) adding a polynucleotide tail to the ends of the segments of the genomic material to generate zero-th order derivative strands;

b) subjecting the zero-th order derivative strands of step (a) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

c) adding a polynucleotide tail to the first order derivative strands;

d) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the first order derivative strands under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (b) and (d) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

In an embodiment of the methods, tagging the segments to generate tagged nucleic acid molecules comprises:

a) adding a polynucleotide tail to the ends of the segments of genomic material to generate zero-th order derivative strands,

b) subjecting the zero-th order derivative strands of step (a) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (a) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

c) subjecting the product of step (b) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (a) under conditions which promote the formation of only one complement, wherein the primers of step (c) have different nucleotide sequences than the primers of step (b), and wherein the polymerase has 3′-5′ proofreading activity,

wherein the primers of at least one of steps (b) and (c) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

In an embodiment of the methods, adding a polynucleotide tail comprises the use of a terminal transferase.

In an embodiment of the methods, tagging the segments to generate tagged nucleic acid molecules comprises ligation of adaptors comprising the tags to at least one end of the segments of the genomic material.

In an embodiment of the methods, the adaptors comprising the tags are ligated to only one end of the segments of the genomic material.

In an embodiment of the methods, the tags comprise a sequence that aids PCR amplification.

In an embodiment of the methods, each tagged nucleic acid molecule comprises one tag.

In an embodiment of the methods, each tagged nucleic acid molecule comprises more than one tag.

In an embodiment of the methods, segments of the genomic material are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication.

In an embodiment of the methods, segments of the cDNA are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication.

In an embodiment of the methods, the maximum copy number of a location on a cDNA library is not less than the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the cDNA library.

An embodiment of the above methods further comprises analyzing mRNA copy number.

In an embodiment of the methods, separating the tagged nucleic acid molecules into a group consisting of hemi-methylated tagged nucleic acid molecules and a group consisting of unmethylated tagged nucleic acid molecules is by cleavage with

methylation sensitive restriction enzymes, partitioning with antibodies, or partitioning with methyl-C binding proteins directed to methylated or hydroxymethylated cytosine.

In an embodiment of the methods, the tagged nucleic acid molecules are subject to hybrid capture prior to PCR or prior to sequencing.

In an embodiment of the methods, each tagged nucleic acid molecule differs at more than one nucleotide.

In an embodiment of the methods, the tag sequences further comprise a sample tag.

In an embodiment of the methods, the tagged nucleic acid molecules are pooled with a plurality of tagged nucleic acid molecules having a different sample tag prior to PCR amplification or prior to sequencing.

An embodiment of the methods further comprises deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads according to sample tag.

In an embodiment of the methods, the tagged nucleic acid molecules are generated from a single species.

In an embodiment of the methods, the tagged nucleic acid molecules are generated from a single organism.

In an embodiment of the methods, tagged nucleic acid molecules are generated from a single cell.

In an embodiment, the single cell is from a needle aspirate of suspected cancer lesions.

In an embodiment, the single cell is from a core biopsy of suspected cancer lesions.

In an embodiment of the methods, the tagged nucleic acid molecules are generated from two or more organisms.

In an embodiment, the tagged nucleic acid molecules are generated from a single cell of each organism.

In an embodiment of the methods, the single species is human.

In an embodiment of the methods, the tagged nucleic acid molecules are generated from two or more species.

In an embodiment, the tagged nucleic acid molecules are generated from a population of microbes.

A further embodiment comprises comparing the genomic copy number information obtained for different species of the population to determine the relative count of those different species in the population.

Also provided is a composition of matter derived from genomic material comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining segments of the genomic material;

b) adding a polynucleotide tail to the ends of the segments of the genomic material to generate zero-th order derivative strands;

c) subjecting the zero-th order derivative strands of step (b) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

d) adding a polynucleotide tail to the first order derivative strands;

e) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the first order derivative strands under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (c) and (e) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

Also provided is a composition of matter derived from genomic material comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining segments of genomic material;

b) adding a polynucleotide tail to the ends of the segments of genomic material to generate zero-th order derivative strands,

c) subjecting the zero-th order derivative strands of step (b) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (b) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

d) subjecting the product of step (c) to a polymerase reaction in the presence of primers

capable of hybridizing to the polynucleotide tail added in step (b) under conditions which promote the formation of only one complement, wherein the primers of step (d) have different nucleotide sequences than the primers of step (c), and wherein the polymerase has 3'-5' proofreading activity,

wherein the primers of at least one of steps (c) and (d) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

Also provided is a composition of matter derived from a mRNA transcripts comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining cDNA from the mRNA transcripts;

b) optionally obtaining segments of the cDNA; and

c) tagging the cDNA or segments of cDNA with substantially unique tags to generate tagged nucleic acid molecules, wherein each tagged nucleic acid molecule comprises

i) one cDNA from step (a) or one segment of the cDNA from step (b) and

ii) a tag.

Also provided is a composition of matter derived from mRNA transcripts comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining mRNA transcripts;

b) subjecting the mRNA transcripts to a polymerase reaction in the presence of primers capable of hybridizing to the polyA tail of the mRNA transcripts under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

c) adding a polynucleotide tail to the first order derivative strands;

d) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (c) under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (b) and d) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

In an embodiment of the above compositions, adding a polynucleotide tail comprises the use of a terminal transferase.

In an embodiment of the above compositions, each tagged nucleic acid molecule comprises one tag.

In an embodiment of the above compositions, each tagged nucleic acid molecule comprises more than one tag.

In an embodiment of the above compositions, segments of the genomic material are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication.

In an embodiment of the above compositions, segments of the cDNA are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication.

In an embodiment of the above compositions, the complexity of the tagged nucleic acid molecules is reduced by hybrid capture.

In an embodiment of the above compositions, each tagged nucleic acid molecules differs at more than one nucleotide.

In an embodiment of the above compositions, the tag sequences further comprise a sample tag.

Also provided is a composition of matter comprising at least two pools of tagged nucleic acid molecules as described herein.

In an embodiment of the above compositions, the tagged nucleic acid molecules are generated from a single cell.

In an embodiment, the single cell is from a needle aspirate of suspected cancer lesions.

In an embodiment, the single cell is from a core biopsy of suspected cancer legions.

In an embodiment of the above compositions, the tagged nucleic acid molecules are generated from two or more organisms.

Also provided is a kit for determining nucleic acid copy number information unaffected by amplification distortion comprising:

a) a terminal transferase, and

b) plurality of substantially unique primers,

wherein the substantially unique primers comprise substantially unique tags, and wherein the substantially unique primers are capable of hybridizing to the polynucleotide tail of a nucleic acid molecule which has a polynucleotide tail added by the terminal transferase.

In an embodiment, the kit further comprises a DNA polymerase having 3′-5′ proofreading activity.

In an embodiment of the kits, the plurality of substantially unique primers comprises 10^n primers, wherein n is an integer from 2 to 9.

In an embodiment, the kits further comprise a second terminal transferase and a primer capable of hybridizing to the polynucleotide tail of a nucleic acid molecule which has a polynucleotide tail added by the second terminal transferase.

In an embodiment of the kits, the tags are six nucleotides long.

In an embodiment of the kits, the tags are 15 nucleotides long.

In an embodiment, the kits further comprise sample tags.

In an embodiment, the sample tags are 2 nucleotides long.

In an embodiment, the sample tags are 4 nucleotides long.

In an embodiment, the sample tags comprise a sample tag set.

In an embodiment of the above kits, the substantially unique tags comprise the sample tags.

Terms

For the purpose of this invention, different words and phrases are defined as follows:

As used herein, the term "adaptor" refers to an oligonucleotide or nucleic acid fragment or segment that can be ligated to a nucleic acid molecule of interest. For the purposes of this invention adaptors may, as options, comprise primer binding sites, recognition sites for endonucleases, common sequences, promoters, tag sequences, and sample tag sequences. Preferably, adaptors are positioned to be located on both sides (flanking) a particular nucleic acid molecule of interest. In accordance with the invention, adaptors may be added to nucleic acid molecules of interest by standard recombinant techniques (e.g. restriction digest and ligation). For example, adaptors may be added to a population of linear molecules, (e.g. a genomic DNA which has been cleaved or digested) to form a population of linear molecules containing adaptors at one and preferably both termini of all or a substantial portion of molecules. The adaptor may be entirely or substantially double stranded or entirely single stranded. A double stranded adaptor may comprise two oligonucleotides that are at least partially complementary. The adaptor may be phosphorylated or unphosphorylated on one or both strands. Adaptors may be used for DNA sequencing. Adaptors may also incorporate modified nucleotides that modify the properties of the adaptor sequence. For example, methylated cytosines may be substituted for cytosines. In an embodiment of this invention the adaptors ligated to genomic DNA to enable cluster generation on the sequencer contain cytosines which were all methylated. This modification protects such adaptors from bisulfite conversion, and is taken into account in the downstream applications and analysis of this invention.

As used herein, the term "amplifying" refers to the process of synthesizing nucleic acid molecules that are complementary to one or both strands of a template nucleic acid. Amplifying a nucleic acid molecule typically includes denaturing the

template nucleic acid, annealing primers to the template nucleic acid at a temperature that is below the melting temperatures of the primers, and enzymatically elongating from the primers to generate an amplification product. The denaturing, annealing and elongating steps each can be performed once. Generally, however, the denaturing, annealing and elongating steps are performed multiple times (e.g., polymerase chain reaction (PCR)) such that the amount of amplification product is increasing, often times exponentially, although exponential amplification is not required by the present methods. Amplification typically requires the presence of deoxyribonucleoside triphosphates, a DNA polymerase enzyme and an appropriate buffer and/or co-factors for optimal activity of the polymerase enzyme. The term "amplification product" refers to the nucleic acid sequences, which are produced from the amplifying process as defined herein.

As used herein, the term "amplification distortion" refers to non-uniform amplification of template nucleic acid molecules.

As used herein, the term "bisulfite-treatment" refers to the treatment of nucleic acid with a reagent used for the bisulfite conversion of cytosine to uracil. Examples of bisulfite conversion reagents include but are not limited to treatment with a bisulfite, a disulfite or a hydrogensulfite compound.

As used herein, the term "bisulfite-converted material" refers to a nucleic acid that has been contacted with bisulfite ion in an amount appropriate for bisulfite conversion protocols known in the art. Thus, the term "bisulfite-converted material" includes nucleic acids that have been contacted with, for example, magnesium bisulfite or sodium bisulfite, prior to treatment with base.

As used herein, the term "sequence capture" or "hybrid capture" refers to a process of hybridizing a "capture probe" to a nucleic acid having a sequence which is complementary to the sequence of the capture probe. A capture probe may be immobilized to a substrate on a solid phase microarray, wherein "substrate" refers to short nucleic acid sequences which are known. Their location on the solid phase microarray may or may not be predetermined. The capture probe comprising a "sequence complementary to the substrate" may be immobilized to the solid phase microarray by hybridizing to its complementary "substrate sequence."

As used herein, the term "clamp" refers to a nucleotide sequence of CC, CG, GC or GG which may be located at the first two nucleotide positions at the 5′ end of a primer, tag, or sample tag, or the last two nucleotide positions at the 3′ end of a primer, tag, or sample tag.

As used herein, the term "comparable number of locations" means that a first genomic region has a number of locations on the genome which is within 25% of the number of locations of a second genomic region. In an embodiment, the first genomic region which has a comparable number of locations to the second genomic region has a number of locations which is within 20%, 15%, 10%, 5%, 1%, or exactly the same as the number of locations of the second genomic location.

As used herein, a subsequence of a tag associated sequence read is "corresponding to" a tag when the subsequence is identical to the nucleotide sequence of the tag.

As used herein, a subsequence of a tag associated sequence read is "corresponding to" a species of a nucleic acid molecule when the subsequence is substantially identical to or substantially complementary to at least about 10, 12, 14, 16, 18, 20, or more nucleotides of the sequence of the species of

nucleic acid molecule. In an embodiment, the subsequence is identical to or fully complementary to at least about 10, 12, 14, 16, 18, 20, or more nucleotides of the sequence of the species of nucleic acid molecule.

The term "CpG site" refers to the CpG dinucleotide.

As used here, the term "CpG island" refers to a region of DNA with a high G+C content and a high frequency of CpG dinucleotides relative to the bulk genome, as further defined at the UCSC Genome Bioinformatics Site at genome.ucsc.edu/index.html?org=Human&db=hg19&hgsid=171216665, and in particular, by annotation in the USCS Genome Bioinformatics Site database (CpG Islands Track or Table: cpgIslandExt).

As used herein, the term "fully complementary" refers to the reverse complement of a nucleic acid sequence.

As used herein, the term "library" refers to a collection of nucleic acid molecules (circular or linear). In one preferred embodiment, a library is representative of all of the DNA content of an organism (such a library is referred to as a "genomic" library), or a set of nucleic acid molecules representative of all of the expressed genes (such a library is referred to as a cDNA library) in a cell, tissue, organ or organism. A library may also comprise random sequences made by de novo synthesis, mutagenesis of one or more sequences and the like. A library may be contained in one vector.

As used herein, the term "mapping" refers to identifying a location on a genome or cDNA library that has a sequence which is substantially identical to or substantially fully complementary to the subsequence of a tag associated sequence read corresponding to a species of nucleic acid molecule, and assigning the tag associated sequence read or the tagged nucleic acid molecule generating the tag associated sequence

read to the location. The nucleic acid molecule may be, but is not limited to the following: a segment of genomic material, a cDNA, a mRNA, or a segment of a cDNA.

As used herein, the term "methylation" refers to the covalent attachment of a methyl group at the C5-position of the nucleotide base cytosine within the CpG dinucleotides of genomic region of interest. The term "methylation state" or refers to the presence or absence of 5-methyl-cytosine ("5-Me") at one or a plurality of CpG dinucleotides within a DNA sequence. A methylation site is a sequence of contiguous linked nucleotides that is recognized and methylated by a sequence specific methylase. A methylase is an enzyme that methylates (i. e., covalently attaches a methyl group) one or more nucleotides at a methylation site.

As used herein, the term "mRNA transcript" refers to the nucleic acid molecule resulting from transcription of DNA.

As used herein, the term "pool" means to combine one plurality of nucleic acid molecules with at least one other plurality of nucleic acid molecules. In an embodiment, tagged nucleic acid molecules are pooled. Pooling may be done after any step in which tagged nucleic acid molecules are generated. In an embodiment, pooling is done prior to PCR and/or prior to sequencing. In an embodiment, tagged nucleic acid molecules generated from a single cell are pooled with tagged nucleic acid molecules generated from a different single cell.

As used herein, the term "probe array" refers to an array of N different nucleic acid molecules deposited on a reaction substrate which serve to interrogate mixtures of target molecules or multiple sites on a single target molecule administered to the surface of the array.

As used herein, the term "read" or "sequence read" refers to the nucleotide or base sequence information of a nucleic acid that has been generated by any sequencing method. A read therefore corresponds to the sequence information obtained from one strand of a nucleic acid fragment. For example, a DNA fragment where sequence has been generated from one strand in a single reaction will result in a single read. However, multiple reads for the same DNA strand can be generated where multiple copies of that DNA fragment exist in a sequencing project or where the strand has been sequenced multiple times. A read therefore corresponds to the purine or pyrimidine base calls or sequence determinations of a particular sequencing reaction.

As used herein, the term "reference genome" refers to a genome of the same species as that being analyzed for which genome the sequence information is known.

As used herein, the term "region of the genome" refers to a continuous genomic sequence comprising multiple discrete locations.

As used herein, the term "representation of DNA" or "representation of a genome" refers to a sampling of the DNA or genome produced by a restriction endonuclease digestion of genomic or other DNA, followed by linkage of adaptors and then amplification with primers complementary to the adaptors.

As used herein, the term "sample tag" refers to a nucleic acid having a sequence no greater than 1000 nucleotides and no less than two that may be covalently attached to each member of a plurality of tagged nucleic acid molecules or tagged reagent molecules. A "sample tag" may comprise part of a "tag."

As used herein, the term "sample tag set" refers to a plurality of unique sample tags of the same length, wherein the nucleotide sequence of each unique sample tag differs from

the nucleotide sequence of any other unique sample tag in the sample tag set at two or more corresponding positions in the sequence. A unique sample tag selected from the sample tag set may be covalently attached to each member of a unique sample consisting of a plurality of tagged nucleic acid molecules in order to identify a tagged nucleic acid molecule as a member of that unique sample.

As used herein, the term "segments of cDNA," refers to the nucleic acid molecules resulting from fragmentation of cDNA.

As used herein, the term "segments of genomic material" refers to the nucleic acid molecules resulting from fragmentation of genomic DNA.

A nucleic acid molecule which contains a sequence of nucleotides identical to a segment of a cDNA or a segment of genomic material comprises a "segment of cDNA" or a "segment of genomic material," respectively.

As used herein, the "sequence complexity" or "complexity" with regards to a population of polynucleotides refers to the number of different species of polynucleotides present in the population.

As used herein, "substantially identical" or "substantially fully complementary" sequences have at least about 80% sequence identity or complementarity, respectively, to a nucleotide sequence. Substantially identical sequences or substantially fully complementary sequences may have at least about 85%, 90%, 95% or 100% sequence identity or complementarity, respectively.

As used herein, the term "substantially unique primers" refers to a plurality of primers, wherein each primer comprises a tag, and wherein at least 50% of the tags of the plurality of

primers are unique. Preferably, the tags are at least 60%, 70%, 80%, 90%, or 100% unique tags.

As used herein, the term "substantially unique tags" refers to tags in a plurality of tags, wherein at least 50% of the tags of the plurality are unique to the plurality of tags. Preferably, substantially unique tags will be at least 60%, 70%, 80%, 90%, or 100% unique tags.

As used herein, the term "tag" refers to a nucleic acid having a sequence no greater than 1000 nucleotides and no less than two that may be covalently attached to a nucleic acid molecule or reagent molecule. A tag may comprise a part of an adaptor or a primer.

As used herein, a "tagged nucleic acid molecule" refers to a nucleic acid molecule which is covalently attached to a "tag."

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range, and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

All combinations of the embodiments of the invention described herein are within the scope of the invention unless clearly indicated otherwise.

Single Cell Copy Number Profiling by 'Sequence Counting' and Sample Tagging.

High throughput sequencers are in effect single molecule sequencers. Because the human genome is sequenced and assembled, a single molecule sequencer is also a single molecule identifier. Therefore, sequencing is also counting, as illustrated in Figure 4 which illustrates how low coverage sequencing can yield an estimate of copy number which is comparable to array hybridization. The distinction for this is that 'sequence counting' can be done on single cells, and, using the multiplex system disclosed herein, relatively inexpensively, in effect converting the high throughput sequencer into a detector of single cells with abnormal genomes. To the sequencing technology two additional features were added: limiting dilution and sample tagging. For single-cell sequencing, the single cells or the nuclei of the single cells are first deposited into separate wells or are kept physically separated by other means, i.e. a gel. The single cells or the nuclei of cells can be deposited in a well by a cell sorter. Alternatively a collection of cells or nuclei can be diluted into a fluid that is then made semi-solid. A unique sample tag is prepared for each well for sequencing, with a separate sample tag per well. After this step, the wells are pooled and sequenced. The sample tag is used to deconvolute the information, allowing a copy number profile to be made for each individual cell.

Protocol: Isolate single tumor cells or single nuclei of the tumor cell, tag and optionally sample tag the DNA of each cell or nuclei, and amplify the tagged DNA to microgram quantities to generate tagged libraries for Solexa sequencing. The isolation of single tumor cells will occur by Fluoresent Activated Cell Sorting by total genomic DNA content, to deposit single nuclei into individual wells.

Alternatively, tumor cells can be isolated by FACS sorting with fluorescent antibodies against breast epithelium markers,

including cytokeratin 8, 18 or 19. Cells are lysed *in situ* and the genome is fragmented by heating. Libraries are constructed from the fragmented genomic DNA. Preliminary experiments were conducted using high-resolution ROMA microarray to quantify whole-genome copy number on DNA amplified using WGA from single SK-BR-3 cells (Figure 5). These experiments demonstrate the feasibility and efficiency of amplifying 6 pg of DNA into microgram quantities to determine copy number by microarray methods, which suggests that the DNA is also suitable for determining copy number by sequencing.

Since sequencing whole tumor genomes from single cells is costly and time consuming, two methods are proposed to stratify the genome and sequence for copy number: Representation Sequencing and Bin Sequencing.

Representation Sequencing

Representation sequencing involves restriction digesting genomic DNA into fragments and sequencing only the stratified population of restriction fragments to determine copy number. This method has the advantage of generating precise restriction fragments that can be reliably prepared as libraries from different individual tumor cells. In this protocol genomic DNA is amplified from a single tumor cell, digested with the DpnII, a second digestion is preformed with a AluI enzyme to remove highly repetitive "Alu SINE elements," sequencing adaptors (Illumina GA, Solexa) with a unique 4 nucleotide sample tag are ligated and the ligated fragments are PCR amplified to generate a sequencing library. *In silico* modeling predicts that the double digest will increase the fraction of unique sequencing reads to 75% from the 55% normally seen in unselected human genome sequencing. The sample tagged DNA libraries are then pooled, and applied to the Solexa flow-cells for cluster amplification and single

read sequencing. Single-end reads are used because they are faster and cheaper than paired-end reads and provide all of the information necessary for 'sequence counting'. Mapping algorithms then align each sequence read with a high quality score (with a read length in excess of 35bp) and an unambiguous sample tag to a specific location on the DpnII restriction map of the human genome. The result is a count of reads at places in the genome, similar to the process demonstrated in Figure 4, except that the data is segregated by sample tag, so that each well receives a copy number profile.

Bin Sequencing

It is clear that sequencing of random size-selected fragment from the genome is a viable alternative. In this method, the DNA from single tumor cells is amplified to generate fragments from 200-2000bp. Blunt-end cloning is then used to ligate adaptors to these fragments, followed by PCR amplification to generate libraries (standard Solexa protocol for single read genomic DNA). However, in addition to this protocol adaptor sequences with 4 nucleotide sample tags are ligated to generate unique libraries from each tumor cell genome. The sample tagged DNA libraries are then pooled, and applied to the Solexa flow-cells for cluster amplification and single read sequencing. The 35bp sequences are then mapped to specific regions of the human genome and deconvoluted using the unique sample tag to determine which sequence reads originated from which tumor cells. The crucial step in this procedure that is different from representation methods is to artificially divide the human genome into "bins" of several kilobases. Break analysis in sequence count data has another degree of freedom compared to what is practiced for array data, namely that the boundaries of the bins can be adjusted so as to minimize variance. Each bin contains a number of

random genomic sequence reads from which a mean value is computed to determine genomic copy number at low sequence coverage.

The particular use of the WGA method does not depend on absolutely uniform amplification across the genome. Useful data can be obtained even if only half of the potential fragments from a single cell were amplified in a given reaction. Additionally, redundancy of data gained from segmentation benefits in identifying breakpoints.

Representation Sequencing vs. Bin Sequencing

A comparison of the two methods reveals the number of samples that can be profiled per sequencing run. Of the 3,149,324 Dpn II fragments in size range 200-800 (size optimal for sequencing) there are 618,629 not cut with AluI and thus available to be amplified. Approximately 75% of the fragment ends, or about 450,000, yield unique mappings and thus provide locations for counting. The overall process is presented as a flowchart in Figure 7.

Assuming 15 million quality reads per Solexa sequencing lane, random sequencing yields about 55% or 8.25 million unique reads per lane. The DpnII/AluI representation should increase the number of unique reads to 11.25 million. Modeling a single flow cell lane with 100kb bins distributed across the genome, the projected results are as follows:

Table 1

# samples	avg reads/bin/sample (random)	avg.reads/bin/sample (Dpn/Alu)
1 sample per lane	267	363
2 samples per lane	133	181
12 samples per lane	22	30

The number of samples (individual cells) to be sequenced per lane, is between 4 and ten. With 8 lanes on a flowcell, 30-80 samples could be profiled at the level of Figure 4 relatively inexpensively.

Finally, the whole genomic copy number (generated by sequencing) will be determined for multiple, individual tumor cells in a single solid tumor. The data will be segmented into sections that minimize variance of copy number, subject to Kolmogorov-Smirnov significance tests, to generate individual tumor copy number profiles. As stated above, an additional degree of freedom, which our algorithms do not yet incorporate, is selecting the "boundary" of the bins. The single cell tumor genome profiles will be compared to study tumor heterogeneity in single solid tumors which may elucidate the progression of genomic events during tumorigenesis.

Varietal counting of nucleic acids

Measuring the absolute or relative concentration of nucleic acid sequences in a sample often suffers from severe stochastic distortions due to differential amplifications or losses during processing and manipulation of the nucleic acids. There is never more information available than the number of molecules of the starting material in the sample

itself. The method described herein is designed to capture the information at the earliest stage, in a form that is then resistant to distortion by further amplification.

Input nucleic acid molecules (0-th order derivatives), or first round copies of them (1-st order derivatives), present in the sample, can be randomly tagged using a large choice of distinct tags. Every tagged molecule becomes essentially unique, the combination of the information in the tag and the information in the nucleic acid, which can later be read by sequencing. The combination of a tag with a 0-th order, 1-st order, or subsequent N-th order nucleic acid molecule is called a "tagged nucleic acid molecule." After amplification or selection or other processing, the number of different tags is counted.

Within a pool of tagged nucleic acid molecules, each tagged nucleic acid molecule is likely unique in the pool when a sufficiently large number of distinct tags is used. Then in subsequent amplifications these unique tagged nucleic acid molecules are amplified to facilitate detection, but no new species of tagged nucleic acid molecules are created. Thus, distorted counts are not created provided that the number of different tagged nucleic acid molecules is counted.

In the disclosed method, each sequence read generated from a tagged nucleic acid molecule comprises two parts, or subsequences. The first part corresponds to the tag, which identifies the tag (and the sample tag if samples are pooled). The second part corresponds to a nucleic acid in the sample which is mapped to a location in the genome (or to a transcript if RNA molecules are being counted). After deconvoluting by sample tag, the number of different tagged nucleic acid molecules mapped to each location is counted. There are two separate methods of counting, and each can be combined for greater accuracy and determination of confidence.

The first counting method is called "maximum tagged nucleic acid molecule number." The number of different tagged nucleic acid molecules at a given location cannot exceed the true (absolute) copy number. Therefore, for a given region comprising multiple locations, the maximum copy number of the region is not less than the maximum number of different tagged nucleic acid molecules mapped to any location in that region. The maximum number of different tagged nucleic acid molecules centered about a moving window of a fixed number of locations can be taken as the measurement of true copy number of the window. This will provide at worst an underestimate of the maximum true copy number for that window, and never an overestimate. The set of maximum number of different tagged nucleic acid molecules is one type of copy number profile.

The counting method described above is most accurate when the processing efficiency is excellent and the number of molecules mapped to each location is less than the number of tags. Under such conditions virtually each molecule in the sample is tagged and counted, and the true count can be derived. But there is a second method.

The second counting method is called "total different tagged nucleic acid molecules," and is useful, for example, when tagging efficiency is low. The total number of different tagged nucleic acid molecules within a region of a fixed number of locations will be, within a statistical counting error, a monotonic function of true copy number, regardless of the efficiency of tagging. Low efficiency of tagging merely increases the statistical error. The relative copy number of a region can be estimated by comparing the total number of different tagged nucleic acid molecules mapped to the region to, for example, the mean value of tagged nucleic acid molecules mapped to other regions of the genome which have a comparable number of locations.

If the number of molecules at a location on a genome or cDNA library exceeds the number of tags, and tagging is too efficient, copy number information can not be recovered. Rather, the total number of tags at each location would merely be measured. There are at least three ways to remedy this condition: 1) diminish the efficiency of the first step of the process, for example by reducing the reaction time; 2) reduce the amount of sample; and 3) increase the total number of tags. For example, if the length of the tag were N nucleotides, there are 4^N possible tags. For N = 15, there are approximately 10^9 tags, easily in excess of the number of molecules per location.

The collection of reads lend themselves to modeling the power of inference. For each location, there exists the number of tagged nucleic acid molecules observed, and for each species of tagged nucleic acid molecule, the number of times it was observed. With a good estimate of the input, the number of genomes, critical parameters can be accurately deduced because the vast majority of the copy numbers are two per genome. The limiting case of single cell analysis lends itself to the most accurate modeling, with the proportion of null reads enabling the inference of the probability, theta, that a single molecule at a location is detected. Theta is a function of the efficiency of tagging, the efficiency of amplification and processing, and the read depth.

Using the language invented of the WGA reaction, in the specific protocol described here, all first order derivative DNA molecules (i.e., first copies) are tagged, with no new tags introduced when subsequent order derivatives are created. This enables the "counting" of original molecules, alleles in the case of genome analysis. This method is referred to herein as "varietal counting." As long as sequence depth is sufficient, subsequent amplification or methods of trapping

that enrich for regions of interest, or the combination, cannot distort the count. Pooling from multiple cells becomes a natural extension of this method, which improves efficiency, increases throughput and decreases costs.

Tags

The tags are nucleotide sequences with constant portions and variable portions. The length of the constant portion and the length of the variable portion may be the same or different. The length of the tags within a plurality of tags is typically, but not necessarily, the same for all tags. In an embodiment, the total length of a tag is less than 100 nucleotides.

The constant portions are used to aid in the tagging of nucleic acid molecules. For example, the constant portion may contain a nucleotide sequence which allows hybridization to a poly-N tail added by a terminal transferase. The constant portion may also be used to aid in manipulation of the tagged nucleic acid molecules. For example, the constant portion may contain a sequence which is a primer binding site useful for PCR amplification. The constant portion may also be used to identify a sample if there are multiple samples being processed in parallel, i.e., the constant portion may contain a sample tag.

The sequence of individual tags does not need to be known prior to generating tagged nucleic acid molecules. A plurality of tags may have variable portions whose sequences are elucidated for the first time during sequencing. The variable portion of a tag may be a sequence of nucleotides where each nucleotide is individually one of A, T, C, or G, or one of any two of A, T, C, and G, or one of any three of A, T, C, and G, i.e. the variable portion of a tag may consist of only two or three species of nucleotides. Tags may be designed such that

the variable portion has a random sequence. Tags may be designed such that the variable portions are constructed from a set of dinucleotides or trinucleotides.

Tags may be associated with nucleic acid molecules by using, singly or in combination, ligation, nick-ligation, terminal transferase, hybridization, priming, and the like. For example, nucleic acid molecules may be cut with a restriction endonuclease(s), treated with a terminal transferase to add a poly-N tail, hybridized to a tag molecule, and then nick ligated to form a tagged nucleic acid molecule. Specific methods of generating tagged nucleic acid molecules are discussed in detail below.

Tagging with the aid of a terminal transferase

Figure 8 illustrates one embodiment of this method, where the N_{10} designates an oligonucleotide having a tag component and a sample tag component. The first six nucleotides (4096 possible sequences), randomly generated, provide the tag component, and the last four nucleotides (256 choices) are chosen to encode the micro-well, and, hence, a sample tag. The lengths of the tag and the sample tag can be changed to suit needs, and are not limited to a total of ten nucleotides. The lengths are chosen for illustration. The sample tag allows pooling, with deconvolution occurring afterwards. The combination of a tag with a nucleic acid molecule from the input sample provides an essentially unique tagged nucleic acid molecule for the first derivative strand, that can only with very low probability be replicated by chance from another like molecule (a chance of roughly 1/N where N is the number of available tags). In the end, multiple copies of sequence-identical molecules in the input sample are each individually counted. In applications to mRNA counting, the length of the tag component can be increased to accommodate possibly thousands of transcripts from the same gene.

Although there are multiple embodiments of the basic method besides the one illustrated in Figure 8, the embodiment illustrated in Figure 8 has several useful design features. First, it avoids the use of ligases (an alternate method for associating a tag with a nucleic acid molecule), which has been found to be an inefficient reaction. Instead, this embodiment uses terminal transferase (TTase), which is a robust enzyme from which high efficiency is expected. Second, once the tag and sample tag are incorporated into the first derivative DNA strand, micro-wells can be pooled and the subsequent steps carried out more efficiently in larger volumes with larger numbers of molecules, possibly with the addition of carrier nucleic acids. Because of a clean-up step, removing free adaptor, no more unique first order derivative strands with tags can be created, and second order strands can be arithmetically expanded if found to be useful. Third, the method extends immediately from DNA to mRNA. Rather than cleaving and adding a polynucleotide tail with terminal transferase, the naturally occurring polyA tail of mRNAs can be utilized. Fourth, it is easy to see how to combine analysis of both RNA and DNA from the same cell with this schema. Instead of tailing DNA with A, it can be tailed with, for example, C, thus distinguishing the DNA from the RNA. DNA and RNA derivatives can either be read together in the same sequencing runs, or separately by amplification using their differing PCR primer adaptors. Fifth, by using a longer sample tag, sequences belonging to a particular cell can be preferentially amplified for deeper study when warranted.

This method can be applied to assessing DNA methylation. After the first order derivative strands are made, the duplex DNA can be pooled from multiple samples. These molecules will be hemi-methylated, and still retain epigenetic marks. Therefore they can then be separated into methylated and unmethylated samples either by cleavage with methylation sensitive

restriction enzymes, or by partitioning with antibodies or methyl-C binding proteins directed to methylated (or hydroxyl methylated) cytosine. Error rates will be measured based on expectations from regions of known methylation state.

Tagging by ligation

In another embodiment of the invention, adaptors with tag(s) can be ligated to sample DNA or RNA that has been converted to DNA. In the second step these molecules can be pooled (or not) and amplified for sequencing. In the third step the numbers of each different tagged nucleic acid molecule of each locus (or mappable sequence read) are compiled, giving statistics from which copy number can be inferred.

In another embodiment, to measure RNA, RNA is first converted to DNA using methods that produce a single double stranded molecule for each RNA in the sample. (For example, prime with oligo dT and reverse transcriptase, followed with random priming and Klenow polymerase.) The procedures for analyzing DNA can then be followed.

In another embodiment, the sample DNA can be sheared and the ends prepared for ligation. However, there are three major advantages to cleaving with one or more restriction endonucleases (RE). The first is that the expected number of tagged nucleic acid molecules at each location can be precisely predicted from the starting number of cells in the sample, or conversely the number of cells in the sample inferred from the expected number of tagged nucleic acid molecules per location. The second is that the expected complexity of the product is reduced, enabling copy number determination from fewer sequence reads. The third are certain advantages in the flexibility and functionality that can be built into the tags.

In an embodiment, sample nucleic acid is cleaved with a specific restriction enzyme and sample molecules are ligated to tagged (and sample tagged if appropriate) oligonucleotide adaptors which contain sequences that allow PCR amplification. There are various designs for these adaptors, and also alternatives to PCR (such as WGA), based on the functionalities built into the tags. Some of these additional functionalities are discussed below.

The ligated molecules now are essentially unique, the ligated molecules each being the combination of a substantially unique tag and DNA sequence to which they were ligated. Further amplification may distort the yields of molecules, but will not create new tags (although some may be lost by statistical processes which are readily modeled during analysis).

Through sequence error during processing, the tag may very occasionally mutate, creating the appearance of a new tagged nucleic acid molecule. But if the set of tags are sufficiently large, the tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting.

For single cells, individual cells are loaded at most one per microwell. The nucleic acid is then prepared in wells, and the molecules tagged. Once tagged they can be pooled for further processing, which greatly improves the uniformity and efficiency of DNA amplification methods.

In yet another embodiment, DNA is cut, and adaptors are ligated to both ends of each fragment, enabling them to be amplifiable by PCR. To avoid adaptor-adaptor self ligation, double stranded adaptors without 5′ phosphorylation can be used, so an adaptor is ligated on one strand only at each end of the cleaved sample DNA. Then the molecules are pooled, and

treated as for representations: the shorter single strand adaptor is melted off at elevated temperature but well below the Tm for the sample duplex, the ends of the double stranded DNA filled in with Klenow polymerase, unligated adaptors removed, and then the sample is PCR amplified.

In the preceding embodiment, adaptors are used not only for tagging but also for amplification. Adaptors are for identifying each molecule individually. They can also be used for amplification, as described above, or for other uses (see below). Because in the above embodiment adaptor ligation at both ends of sample fragments is required for amplification, the yield may be diminished. To improve yield, the method can work with molecules that have an adaptor at one end only.

In one embodiment, the reactions are performed as before, but tags do not contain sequences enabling PCR. Prior to PCR, but after an optional pooling, fresh adaptors (different composition and without tags) are ligated so that molecules with only a single tag adaptor can be amplified and eventually counted. If the original tag has a selection sequence, molecules with the tag adaptor before sequencing can be optionally enriched by hybrid selection.

In another embodiment, initial adaptors are designed with a phosphorylated 5′ end and a 3′ dideoxy end, so that the initial ligation occurs to the opposite strand as described in the embodiment above. (Instead of using an RE with a 5′ overhang, one which leaves a 3′ overhang may be preferred.) After removal of unligated adaptors, there follows several rounds of arithmetic amplification, followed by tailing molecules with dT using terminal transferase, and amplification of the processed sample DNA by PCR.

In another embodiment, DNA from sample is labeled as before, pooled if required, and unligated adaptors removed from the

reaction. The reaction is subject to whole genome amplification (WGA), and the product of WGA is used to make sequencing libraries. For this embodiment, the initial adaptors may also contain: (A) cleavage sites for ease of making sequencing libraries; and (B) a sequence large enough for optional enrichment by hybrid selection prior to making libraries for sequencing.

In the embodiments just described, it is assumed that the tag is double stranded. The production of a great variety of double stranded molecules is not completely straightforward. In one embodiment, single strand DNA is synthesized as type I and type II. Type II has three sets of functionalities A, B, C, and D. Functionalities B contain the tag sequence, C the adhesive ends with a RE site, and D the buffer. The B will contain some length of runs with random sequence, for example 10 nucleotides with a total complexity of 4^{10}, or about 10^6 possible sequences. Type I oligo will be complementary to type II at functionality A, the two joined and annealed, and then extended with polymerase to create a double stranded molecule. After cleavage with the RE site, the resulting double stranded molecule is the tag used for the subsequent tagging of the sample.

Additional methods for producing single and double stranded oligonucleotides suitable for use as tags are known in the art, for example, in U.S. Patent Nos. 5,639,603 and 7,622,281, U.S. Patent Application Publication No. 2006/0073506 and Parameswaran et al. (2007) (7,5,8,4).

Nick-ligation

In this embodiment of the invention, 3'OH ends of nucleic acid molecules, e.g., segments of genomic material or mRNA transcripts, are first extended with terminal transferase, adding a poly-N tail. Primer adaptors are then annealed to the

poly-N tails and the resulting duplex with a nick is sealed with DNA ligase. This series of reactions is much more efficient than a single step double stranded ligation. The resulting product is amplified by PCR. This method has been successfully used with as little as 1ng of DNA. Tagged nucleic acid molecules generated using the nick-ligation method can be generated from a single cell DNA, and then pooled prior to PCR. Pooling from 100 cells yields the DNA concentration needed for successful amplification. Sample tags can be added in the nick ligation step, and this is readily achieved (see Figure 9).

Technology for inexpensive assay of regional markers

The above description is of methodology designed to measure copy number and mutational loads throughout much of the genome in single cells. But the application of discoveries, once made, of predictive markers for outcome or therapeutic response will not require whole genome information. Our present outcome markers are in fact copy number markers at very specific loci. Essentially the same methodology as disclosed hereinabove can be employed to make these assessments very affordable. Consider, for example, the case where it is desirable to assess a large study for the predicative power of a set of N markers, and these markers are copy number markers that can be assessed by varietal counting. In principle, sample coding, pooling, and parallel capture and sequencing can be used to assay a large number of samples in a single sequencing lane. The major difference is that we are not restricted to minute quantities of DNA, so WGA is not needed, and assays will be more robust. We have shown in our autism work that excellent copy number data can be obtained from read depth after capture. Thus we can use direct library preparation with just sample tags. The target area for capture is likely to be different and smaller than the exome. Thus we

can pool more samples per sequencing lane, and the sequencing costs for assaying hundreds of markers in hundreds of samples can be reduced. Of course, there are costs associated with the development and testing of the capture reagents, and the cost of the capture itself, and these are not negligible, but if a test were to come into widespread clinical use, it would be inexpensive, and this is one of our major objectives. There is a clear alternative, namely creating a bank of region specific PCR primers with tags and sample tags. The tags would be necessary because random unique ends created by shearing would not be available for counting based methods. This alternative plan could be less expensive and more robust than capture (see Figure 10).

Single cell RNA measurements

Several methods have now been published whereby researchers have profiled the RNA content of single cells by sequencing (Tang et al., 2009). This is potentially a very powerful method for analysis of tumor cells. A varietal counting method could be very useful for RNA profiling from single cells, and for the same reasons that it is useful with DNA. When variety is not introduced by nucleic acid processing varietal counting provides a way to avoid the distortions created by PCR. RNA and DNA can be analyzed from the same cells. The DNA analysis enables us to cluster cells into stromal and tumor subpopulations, and this in turn facilitates the interpretation of the RNA profiling. As an example of utility, suppose one is interested in searching thousands of circulating cells, or cells from a biopsy, or from the margins of a tumor, for rare tumor cells. DNA copy number can facilitate its identification, and the RNA from that cell can then be reliably used to infer additional properties, such as the tissue of origin. This combination is especially powerful

for the early detection of the new incidence or recurrence of cancer.

Examples

Methylation sequencing

Currently, high throughput sequencing requires physical purification of sub-genomic regions of interest in order to obtain high coverage of those regions. The method of sequence capture has been applied to examine methylation in large sets of CpG islands at the sequence level. Methylation sequencing is based on the conversion of C residues to T using bisulfite reagents, with methylated C's detected as those protected from C to T conversion. This means either that sequence capture must take place before bisulfite treatment, which requires more starting DNA than is available for patient specimens, or that sequence capture must be designed to accommodate the C to T conversion. The bisulfite based sequencing method used herein adopts the latter and so is suitable for high throughput single molecule sequencing by either the Illumina or Roche 454 methods, using as little as 100 ng of input DNA. The sequencing method depends on hybrid capture of bisulfite treated DNA followed by sequencing through the Illumina Solexa sequencer and mapping back to the genome using an algorithm developed Dr. Andrew Smith (19). It was observed that CpG islands can exhibit multiple different levels of methylation, from imprinted (allelic) to randomly partially methylated, to completely methylated or unmethylated. In particular, one observation that is important for this invention is that many islands switch from completely unmethylated in normal tissues to virtually completely methylated in matched tumor tissue ("DNA-methylation switch domains"). Figure 3 shows three examples of the simplest cases in normal cells versus the breast cancer cell line MDA-MB-231: stably unmethylated (A and B); the ALX gene, switched from unmethylated to completely

methylated (C and D); and a case, SSTR4, where only a segment of the island is switched (E and F). This complete switch makes it possible to detect rare tumor cell DNA in bodily fluids or other cell populations using nested PCR of bisulfite treated DNA and opens up the possibility of a creating a method for the early detection of recurrence in the form of circulating metastatic cells.

Comparative genomic hybridization (CGH) by high throughput sequencing

Until now the most economical method for high resolution genomic analysis has employed some form of microarray. The rapid rise of 'next generation' DNA sequencing is changing that landscape. Both the Illumina (Solexa) and Roche 454 instruments can provide millions of individual sequence reads randomly distributed across any input DNA (Craig et al., 2008). The depth of coverage of these technologies depends on the total length of the input DNA, from whole genome (large breadth, lower depth) to narrowly focused regions achieved by hybrid capture of specific sequences (narrow breadth, higher depth) (Albert et al., 2007; Hodges et al., 2007; Okou et al., 2007). Converting sequencing reads to copy number analysis is a matter of mapping reads and then put them into 'bins' of a certain size, depending on the purpose, counting up the numbers in the bins and performing appropriate statistical analysis to define copy number change breakpoints.

Sequence counting was applied to the degraded formalin-fixed paraffin-embedded (FFPE) DNA that was available from retrospective clinical trials with very encouraging results. Figure 4 displays a comparison of microarray and sequence counting results in a region around Her2 on chromosome 17 for a 10 year old paraffin-embedded clinical trial sample JZ33. The gray and orange points are (respectively) the raw ratio data for 244K Agilent microarray and one lane of Solexa

sequencing reads divided into 30K bins. Note that the sequencing (orange) track shows significantly less noise. The green and blue lines are the result of segmenting each data type. The segments are generally concordant, but the sequence counting method reveals a somewhat more detailed pattern. Another feature of note from Figure 4 is the robustness of our segmenting program, irrespective of the variation of noise in the two sets of raw data.

The efficacy of sequence counting on FFPE DNA and the rapidly decreasing cost of DNA sequencing in general provides an opportunity to convert our previous microarray methods to a highly flexible and scalable platform for breast cancer genome diagnostics. Both the breadth of DNA to be sequenced and the size and location (and therefore resolution) of individual bins can be easily adjusted to fit the particular loci to be assayed.

Single cell microarray and sequencing

A representation of DNA amplified from single cells was used for genomic profiling by 'sequence counting'. As a preliminary step in developing that technology, DNA was amplified from batches of 1, 10 and 100 cells of the cell line SKBR3 using the Whole Genome Amplification (WGA) Kit from Sigma-Aldrich and compared these amplified representations to equivalent microarrays on the same format done with a standard SKBR3 DNA prep. Individual cells were picked from adherent culture dishes using a cell transfer micropipette. After random WGA1 amplification the DNA preps were digested with DpnII and AluI, adaptors added and only DpnII fragments without AluI sites were amplified by PCR. These representations were labeled and applied to ROMA custom microarrays with 390,000 probes designed to detect DpnII fragments of appropriate size across the genome. The idea was to test how reproducible this two step process would be when

only 2-6 chromosomes are present in each single cell preparation (SKBR3 is roughly triploid).

The results are shown in Figure 5, presenting a comparison of the segmented profiles of a batch preparation of SKBR3 DNA (Figure 5A) against our normal male reference cell line (SKN-1) and three independent single cell DNAs (Figure 5 B,C,D). A visual inspection of these profiles makes it clear that after segmentation, the results for single cells are virtually identical to a standard DNA, leading us to have confidence that sequencing DNA from a representation will yield useful results. Although the raw ratio data is not presented here, we note that the standard deviation of the ratio data is much higher for the three single cell experiments (0.706, 0.725, 0.676) than for a batch DNA preparation (0.313). The extra noise does not adversely affect segmentation, although in certain regions very fine detail may be lost (red arrow in Figure 5A). This is comparable to other WGA1 experiments such as the one depicted in gray in Figure 4. In this light it is also worth noting that our particular use of the WGA1 method does not depend on absolutely uniform amplification across the genome. We benefit from the redundancy of data that we gain from segmentation to identify breakpoints. Even if only half of the potential fragments from a single cell were amplified in a given reaction, we would still obtain useful data.

Sequencing across chromosome breakpoints

One of the methods for the detection of rare tumor cells, in lymph nodes, blood or other bodily fluids is the amplification or sequencing of unique breakpoints resulting from deletions and/or translocations that occur during breast tumor development. Although events such as deletions and duplications are apparent from array CGH, the actual structure underlying the copy number changes is not.

The DNA sequences surrounding 22 breakpoints from two breast cancer cell lines were enriched by hybrid capture on custom microarrays as described by Hodges et al (20). Following hybrid capture, the enriched DNA was amplified and prepared for 'paired end' sequencing on the Illumina GA2 instrument. Paired end sequencing yields approximately 36 bp of sequence from each end of a single DNA molecule (after preparation for sequencing, each molecule is approximately 200 bp in length), and those sequences are then mapped back to the consensus genome. For a molecule from a normal, non-rearranged region the two matched reads should map approximately 130 bp apart. In contrast, at the edges of a deletion, the two reads from a single molecule would be separated on the map by the width of the deletion, or in the case of a translocation, would map to another chromosome. These are referred to as 'bridging fragments' because they connect regions not normally adjacent to one another. Examples of two such bridging fragments are shown at the top of Figure 6, along with the original CGH pattern, and graphs of the distance between paired ends (blue) and the total number of reads (red) across the capture region (X axis). By mapping the exact location of a breakpoint, highly sensitive and specific probes that will distinguish tumor cells from large numbers of normal cell can be prepared. Of 22 regions displaying deletions captured from cell lines T47D and MDA-MB-436, 15 behaved as simple deletions from which unique 'bridging fragments' could be identified as in Figure 6. Two additional sites 'jumped' to different chromosomes indicating translocations. The other 5 sites involved repeated sequences on one of the paired for which the identification of the exact breakpoint was not possible and which would not be suitable for creating unique probes.

Copy number profiling using varietal tags on restriction enzyme fragments.

As one illustration of varietal counting, copy number information was obtained using a "total different tagged nucleic acid molecules method.", DNA fragments were first associated with tags by using terminal transferase and nick-ligation (Figure 9). Genome DNA was obtained from the cell line SKBR3. DNA (2µg) was digested by NlaIII, resulting DNA fragments with 4bp, "CATG", 3′ overhangs. This 3′OH end was extended with terminal transferase by adding a poly-A tail. One of primer adaptors was designed to have tags, 12 Ts and CATG at the 3′ end, so it could be annealed to the 3′ ends of the DNA fragments with a nick site (Figure 9, Product 3). This nick site was ligated by DNA ligase, forming duplex DNA fragments with tags. Another primer adaptor was then added to these duplex DNA fragments by one cycle of PCR (Figure 9, Step 5), allowing the resulting products of this reaction to be further amplified by PCR, followed by sequencing (Illumina/Solexa). Then, by mapping the subsequence of each tag associated sequence read to a location on the genome, the number of DNA fragments (assigned to the same genomic location) with different tags was counted.

We have previously obtained copy number profiles of SKBR3 genomic DNA from a million cell library, by sequencing and sequence counting. Figure 11 compares the use of varietal counting (a "total different tagged nucleic acid molecules method") with 'sequence counting' for analyzing copy number data, genome-wide (Figure 11A) and partial-genome (Figure 11B). The essentially equivalent result obtained using varietal counting illustrates that by adding varietal tags to DNA fragments before PCR one can use varietal counting as described herein to reliably obtain copy number information unaffected by amplification distortion.

Data analysis for the procedure described above employed a modification of the 'bin-counting' method because the NlaIII restriction sites are not distributed evenly in the genome. Therefore, in order to ensure equal weight for each of the 50K bins, the bin boundaries for this experiment were designed to encompass and equal number of NlaIII fragments sized between 100bp and 250bp, the size range from which the Illumina libraries were made.

Discussion

Single cell data is much more informative than data obtained from multiple cells, for example from array hybridization of multiple sections of a primary tumor. First, one can afford to analyze many more genomes by multiplex single cell sequencing than by array hybridization (on the order of a hundred single cells versus a dozen sections). Second, one is able to directly assess the exact proportion of cells in a region of a tumor that are malignant. Third, one is able to make a far more detailed analysis of the temporal order of genetic lesions, since one will not be looking at the average state of a population. Fourth, one is able to assess whether tumor heterogeneity is of the anatomically segregated or the co-habitation type, or both.

The invention described herein may be used to determine the original genome copy number (or the gene expression profile) of a sample without amplification distortion. All measurements of copy number or gene expression, especially involving multiple samples, are potential applications. Samples can be nucleic acids derived from single cells or populations of cells. The invention can be used to study cellular heterogeneity in tumors or normal populations of cells.

The invention may be used to generate a genomic profile of a cell, e.g., a cancer cell, or population of cells. From the

genomic profile it can be determined if specific genes are amplified or deleted. When the sample is derived from expressed RNA, and the regions are expressed genes, the relative counts comprise an expression profile. From the expression profile the tissue of origin of a cancer cell can be identified. When the sample is a mixture of genomes from different species, and the genomic regions distinguish the different species, the relative counts comprise a census of those different species. For example, from a census we can determine the population of microbial flora and relate the same to disease.

One of the advantages of the use of tags is that it allows the use of restriction endonuclease fragments in genome analysis. Counting methods for genome copy number determination use counts of independent reads. Two reads are not considered independent if they are the result of DNA amplification occurring during sample processing. Typically, this entails shearing sample DNA fragments, and the position of ends of the fragments are used to disambiguate PCR duplicates. If two DNA reads have the same ends, they could be PCR duplicates, and not independent, so they are counted as only one true read. One cannot disambiguate restriction fragments this way, because two reads of the same fragment will have the same ends. However, by the addition of tags, independent reads can be distinguished, if they are added before any amplification step, as they will have different tags. By contrast, if two reads of the same genome region have the same tag, they are highly likely to be PCR duplicates, and not independent.

The ability to use sequence of restriction fragments in genome analysis can be exploited to reduce the cost of determining copy number profile, much as performing ROMA facilitates genome analysis. By size selection of fragments, one can sample the genome at greater depth at fewer loci, and still obtain a high resolution copy number profile but with fewer

reads and therefore at lower cost. This is the essence of representation, and results in complexity reduction, the central element of ROMA. In ROMA, the analysis of the representation is done by hybridization to arrays, and here the representation is analyzed by sequencing.

Further complexity reduction can be achieved by sequence capture. The sequence capture can be designed specifically for the fragments that can be predicted by in silico methods to map to the regions where one wants copy number mutation. In this way one can target special regions of the genome, such as the exome, or known cancer genes. Very little sequence of the sample is then needed for copy number determination, and samples can be multiplexed at a great cost saving.

The invention disclosed herein may also be used to determine the proportion of components in a mixture. For example, suppose one possesses a set of reagents, such as antibody molecules, that bind to a set of substrates, such as different proteins, and one desires to detect the relative proportion of those substrates in a sample, such as blood. First, one covalently combines a tag having a sample tag with each reagent, where the sample tag portion identifies the reagent, and the varietal tag will be used in counting. The tagged reagents are then combined with the sample, and reagents that combine with substrates are physically separated. For example, the substrates may be biotinylated before being mixed with reagents, then reagents combining with substrates separated by avidin affinity chromatography. The tags are amplified by PCR and sequenced, effectively yielding relative counts for each reagent species and therefore each substrate. In this case, the constant portions of the tags include the sample identifier and nucleotides used for amplification.

The invention provides the following advantages: (1) the method is simple; (2) with statistical analysis the confidence

of a measurement can be determined with great accuracy; (3) this is a sequence based method, which in the long run will be cheaper than arrays; (4) long read lengths are not necessary, providing savings; (5) because tagged nucleic acid molecules are counted, many processing methods that create distortion in yields can be applied without major loss in the tagged nucleic acid molecule count; (6) among these processing methods are hybrid selection (aka capture microarrays), which restrict the sequence information to regions of importance, and thus reduce cost by reducing the total number of reads per sample needed for determination of the desired information; (7) the molecules from one sample can be combined with tags and a sample tag, creating sample tagged nucleic acid molecules which can then be pooled, and after processing and sequencing, the sample tags decoded, giving a profile for each sample; (8) pooling adds efficiency and uniformity; (9) the samples can be individual cells, yielding large numbers of single cell measurements cheaply.

The invention described herein has clinical applications as described above, including: (1) determination of the genomic heterogeneity of tumors; (2) detection of tumor cells in needle biopsies, in particular an assessment of the heterogeneity of the cells in a biopsy; (3) assessment of the spread of a cancer to regional lymph nodes; and (4) detection of malignant cells in sites such as blood and bone marrow. The presence of cells with the molecular signature of the primary in the blood or bone marrow opens up the possibility of using more general single cell/molecule assays as a first line of defense in the early detection of cancer, i.e. breast cancer in women at risk.

When there is radiological evidence of a breast mass, the patient most commonly undergoes fine needle biopsy, which is examined by the pathologist who makes an assessment of the

malignancy of the mass. Because needle aspiration destroys the histology of the biopsy, one of the pathologist's canonical tools for assessing malignancy is not available. Single cell sequencing would not only more accurately predict the presence of malignant cells, but also give what we might call "genomic staging." Is the tumor a simplex type of complex type? Is it mongenomic or polygenomic? Are there critical loci that are amplified or deleted that might immediately suggest a preoperative therapy?

The single cell/molecule approach allows the assessment of the spread of cancer to regional lymph nodes and to establish the DNA-methylation states at switch regions.

Successful application of single cell/molecule detection in the above contexts will lead to application to the detection of cancer recurrence, and the measurement of cancer load. Detection of recurrence at the earliest possible time may prolong survival for a large class of patients by earlier intervention than they would otherwise receive. Moreover, if cancer load were monitored in the patient, even before the site of the cancer growth is discernible by imaging, then one could measure the response of the cancer to a variety of therapeutic measurements. That is, the most effective choice of therapy could be determined empirically in the patient.

Additional applications exist in the diagnosis and selection of treatment for patients with auto-immune diseases, and in vitro fertilization (IVF) screening of pre-implant embryos for genetic defects such as trisomy-21.

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The disclosures of the following references in their entireties are hereby incorporated by reference into this application.

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If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $75.00 electronic filing fee, $380.00 examination fee, $330.00 utility search fee, and $70.00 Petition fee for a small entity, is deemed necessary in connection with the filing of this Preliminary Amendment and the accompanying continuation application. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

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Assignment of Non-Provisional Application

In consideration of One Dollar ($1.00), and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the undersigned,

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VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
(U.S. Serial No. 13/278,333, filed October 21, 2011, claiming the benefit of U.S. Provisional Application Nos. 61/510,579, filed July 22, 2011 and 61/406,067, filed October 22, 2010)

and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for U.S. Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

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Agree *that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives; and*

Covenant *with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.*

Date: 11-16-11

Witness: _____ [signature]

Vladimir Drozdeff [printed name]

102 Cleveland Dr [address]

Centerport, NY 11721

_____ [L.S.]
James Hicks

[signature] [LS]
Nicholas Navin

Date: 11-14-2011
Witness: [signature]
Jill Waters [printed name]
1515 Holcombe Blvd [address]
Houston TX 77030

[LS]
Jennifer Troge

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[LS]
Zihua Wang

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[LS]
Michael Wigler

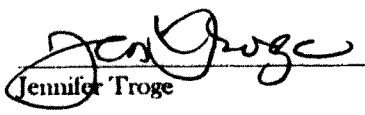
Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[LS]

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

_____ [LS]
Nicholas Navin

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____


_____ [LS]
Jennifer Troge

Date: Nov 16, 2011
Witness: [signature]
Vladimir Drezdoff [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721


_____ [LS]
Zihua Wang

Date: 11/16/2011
Witness: [signature]
Vladimir Drezdoff [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721


_____ [LS]
Michael Wigler

Date: 11/16/2011
Witness: [signature]
Vladimir Drezdoff [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721

_____ [LS]

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

Petition Under 37 C.F.R. § 1.84(a)(2) to Accept Color Drawings Filed

This Petition is submitted under 37 CFR § 1.84(a)(2) to accept the colored Figures which are being filed herewith.

The subject application is being filed with one (1) set of color drawings consisting of fifteen (15) sheets containing Figures 1-11. Such color drawings are necessary because certain features of the Figures are referenced by color in the specification and/or would not be identifiable or distinguishable in black and white.

For example, Figures 3, 4, 5, and 11 show data in a graphical form which cannot be adequately represented in black and white. Figures 8-10 use colors to differentiate strands of nucleic acid molecules and to identify their source.

In accordance with the guidance set forth in Section H of "LEGAL FRAMEWORK FOR EFS-WEB (06APRIL11)" published by the U.S. Patent and Trademark Office at www.uspto.gov/patents/process/file/efs/guidance/New_legal_framework.jsp, the requirement for three (3) sets of color drawings under 37 CFR §1.84(a)(2)(ii) is not applicable to color drawings submitted via EFS-Web. Therefore, applicants are submitting herewith via EFS-Web only one (1) set of such color drawings.

Reference to Color Figures in Specification

In accordance with 37 CFR §1.84(a)(2)(iii), the subject specification contains a paragraph immediately after the section heading titled "Brief Description Of The Figures" stating:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Applicants maintain that this Petition complies with the requirements of 37 CFR § 1.84(a)(2), and respectfully request that this Petition be

granted and the sheets of colored figures filed with the subject application be accepted.

Fee for Filing a Petition under 37 CFR § 1.84(a)(2)

Pursuant to 37 C.F.R. § 1.84(a)(2)(i), a fee of $70.00 is required for filing this Petition for accepting color drawings. Accordingly, authorization is hereby given to charge the amount of SEVENTY DOLLARS ($70.00) to Deposit Account No. 03-3125.

Applicants maintain that this Amendment and Petition complies with the requirements of 37 CFR § 1.84(a)(2), and respectfully request that this Petition be granted and the color drawings filed with the subject application be accepted.

Docket Number: 5981/81503-A/GJG/ACK

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

the specification of which:
(check one)

____ *is attached hereto.*

_X_ *was filed on* October 21, 2011 *as*

Application Serial No. 13/278,333

and was amended October 21, 2011
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International Application which designated at least one country other than the United States, listed below. I have also identified below any foreign application for patent or inventor's certificate, or PCT International Application having a filing date before that of the earliest application from which priority is claimed:

Prior Foreign Application(s)			*Priority Claimed*	
Number	*Country*	*Filing Date*	*Yes*	*No*
N/A			—	—
			—	—
			—	—
			—	—
			—	—

JPW Rev. 8/13/08

IPR2025-01353
CSHL EX2001

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

Provisional Application No.	*Filing Date*	*Status*
61/510,579	July 22, 2011	Pending
61/406,067	October 22, 2010	Pending

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s), or Section 365(c) of any PCT International Application(s) designating the United States listed below. Insofar as this application discloses and claims subject matter in addition to that disclosed in any such prior Application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56, which became available between the filing date(s) of such prior Application(s) and the national or PCT international filing date of this application:

Application Serial No.	*Filing Date*	*Status*
N/A		

And I hereby appoint

Gary J. Gershik (Reg. No. 39,992); John P. White (Reg. No. 28,678); Christopher C. Dunham (Reg. No. 22,031); Norman H. Zivin (Reg. No. 25,385); William E. Pelton (Reg. No. 25,702); Robert D. Katz (Reg. No. 30,141); and Paul Teng (Reg. No. 40,837).

and each of them, all c/o Cooper & Dunham LLP, 30 Rockefeller Plaza, 20th Floor, New York, New York 10112, my attorneys, each with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith and to file any International Applications which are based thereon under the provisions of the Patent Cooperation Treaty.

Please address all communications, and direct all telephone calls, regarding this application to:

Gary J. Gershik, Esq. *Reg.No.* 39,992
Cooper & Dunham, LLP (Customer Number 23432)
30 Rockefeller Plaza
20th Floor
New York, New York 10112
Tel. (212) 278-0400

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.

Full name of sole or first joint inventor James Hicks
Inventor's signature _____ *Date of signature* 11-16-11
Citizenship US
Residence 3 Great Meadow Road, Locust Valley, NY 11560
Post Office Address Same as above

Full name of additional joint inventor (if any) Nicholas Navin
Inventor's signature _____ *Date of signature* _____
Citizenship US
Residence 1621 Wichita St., Houston, TX 77004
Post Office Address Same as above

Full name of additional joint inventor (if any) Jennifer Troge
Inventor's signature _____ *Date of signature* 11.16.11
Citizenship US
Residence 100 Simcoe St., Oyster Bay, NY 11771
Post Office Address Same as above

JPW Rev. 8/13/08

Full name of additional joint inventor (if any) Zihua Wang

Inventor's signature _____ *Date of signature* 11/16/11

Citizenship China

Residence 13 Meadowlawn St., Huntington, NY 11743

Post Office Address Same as above

Full name of additional joint inventor (if any) Michael Wigler

Inventor's signature _____ *Date of signature* 11/16/2011

Citizenship US

Residence 52 Snake Hill Road, Cold Spring Harbor, NY 11724

Post Office Address Same as above

Full name of additional joint inventor (if any) _____

Inventor's signature _____ *Date of signature* _____

Citizenship _____

Residence _____

Post Office Address _____

Full name of additional joint inventor (if any) _____

Inventor's signature _____ *Date of signature* _____

Citizenship _____

Residence _____

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Docket Number: 5981/81503-A/GJG/ACK

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VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

the specification of which:
(check one)

____ *is attached hereto.*

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Prior Foreign Application(s)			*Priority Claimed*	
Number	*Country*	*Filing Date*	*Yes*	*No*
N/A			—	—
			—	—
			—	—
			—	—
			—	—

JPW Rev. 8/13/08

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N/A		

And I hereby appoint

Gary J. Gershik (Reg. No. 39,992); John P. White (Reg. No. 28,678); Christopher C. Dunham (Reg. No. 22,031); Norman H. Zivin (Reg. No. 25,385); William E. Pelton (Reg. No. 25,702); Robert D. Katz (Reg. No. 30,141); and Paul Teng (Reg. No. 40,837).

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20th Floor
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Tel. (212) 278-0400

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Full name of additional joint inventor (if any) Nicholas Navin

Inventor's signature Nicholas E Navin *Date of signature* 11-14-2011

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Residence 1621 Wichita St., Houston, TX 77004

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Full name of additional joint inventor (if any) Jennifer Troge

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Citizenship US

Residence 100 Simcoe St., Oyster Bay, NY 11771

Post Office Address Same as above

Full name of additional joint inventor (if any) Zihua Wang

Inventor's signature _____ *Date of signature* _____

Citizenship China

Residence 13 Meadowlawn St., Huntington, NY 11743

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Full name of additional joint inventor (if any) Michael Wigler

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Citizenship US

Residence 52 Snake Hill Road, Cold Spring Harbor, NY 11724

Post Office Address Same as above

Full name of additional joint inventor (if any) _____

Inventor's signature _____ *Date of signature* _____

Citizenship _____

Residence _____

Post Office Address _____

Full name of additional joint inventor (if any) _____

Inventor's signature _____ *Date of signature* _____

Citizenship _____

Residence _____

Post Office Address _____

Electronic Acknowledgement Receipt

EFS ID:	35085990
Application Number:	16269818
International Application Number:	
Confirmation Number:	8088
Title of Invention:	Varietal Counting of Nucleic Acids for Obtaining Genomic Copy Number Information
First Named Inventor/Applicant Name:	James Hicks
Customer Number:	23432
Filer:	Gary J. Gershik/Darren Haber
Filer Authorized By:	Gary J. Gershik
Attorney Docket Number:	81503-AAA/GJG/ADR
Receipt Date:	07-FEB-2019
Filing Date:	
Time Stamp:	13:00:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$855
RAM confirmation Number	020719INTEFSW00012765033125
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal of New Application	190207_81503-AAA_Transmittal_Letter_ADR.pdf	129122 7a09e5f56f4826edf3db43036c3b786a0669b99f	no	3
Warnings:					
Information:					
2	Application Data Sheet	190207_81503-AAA_Application_Data_Sheet_ADR.pdf	1823367 5d3b7781dce7e061d86c3b456d412e8272552e95	no	10
Warnings:					
Information:					
3		190207_81503-AAA_Preliminary_Amendment_ADR.pdf	221492 9a0030d48a4360bac4943c8a2fff31bc244bd445	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Applicant Arguments/Remarks Made in an Amendment	2	4
A petition from Applicant to accept Color Drawings or Color Photographs	5	6
Preliminary Amendment	7	7

Warnings:					
Information:					
4	CRF Statement Paper and CRF are the same	190207_81503-AAA_Statement_Compliance_ADR.pdf	42502 d180c7fbffc21c3f0c17e621050b554a0f822f7b	no	1
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Information:					

5	Drawings-other than black and white line drawings	190207_81503-AAA_Final_Figures_ADR.pdf	3617729 a368d88afec4ad351e9916ded463848b4fdc0701	no	15
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The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
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6		190207_81503-AAA_Specification2_ADR.pdf	344780 c40adc38f3f046370838b24a0367d9df732abe94	yes	88

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	70
	Claims	71	87
	Abstract	88	88

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9	Assignee showing of ownership per 37 CFR 3.73	190207_81503-AAA_Assignment_ADR.pdf	256867 51c8d732de054193eebc2101293e51b2990204d2	no	4
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Warnings:	
Information:	
Total Files Size (in bytes):	6978336

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.

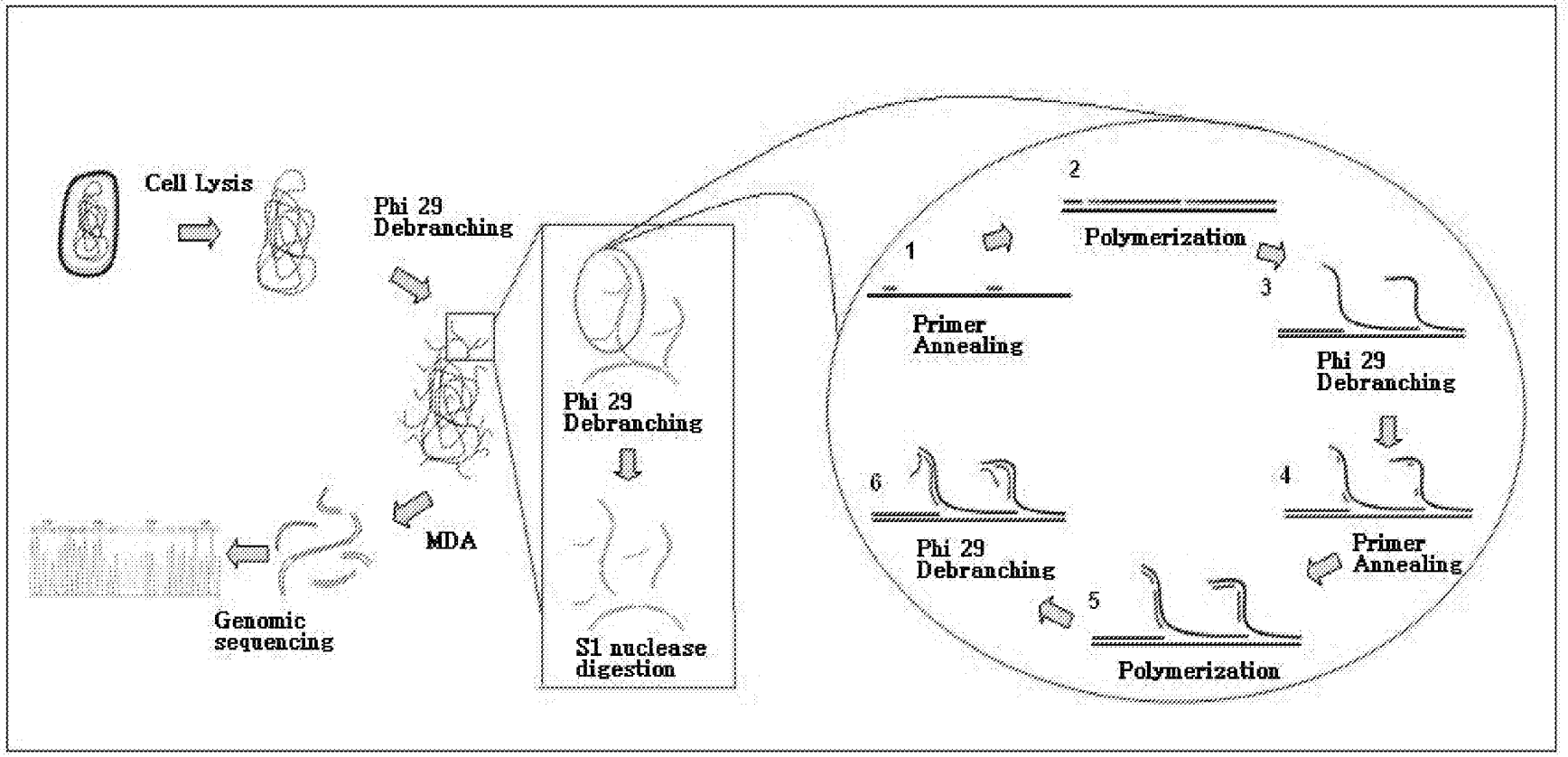


Fig. 1

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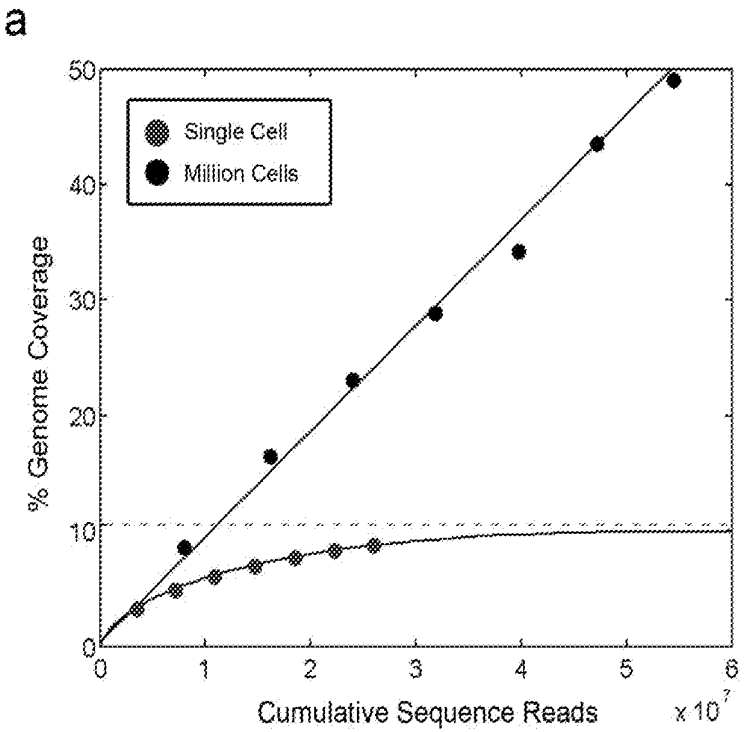


Fig. 2

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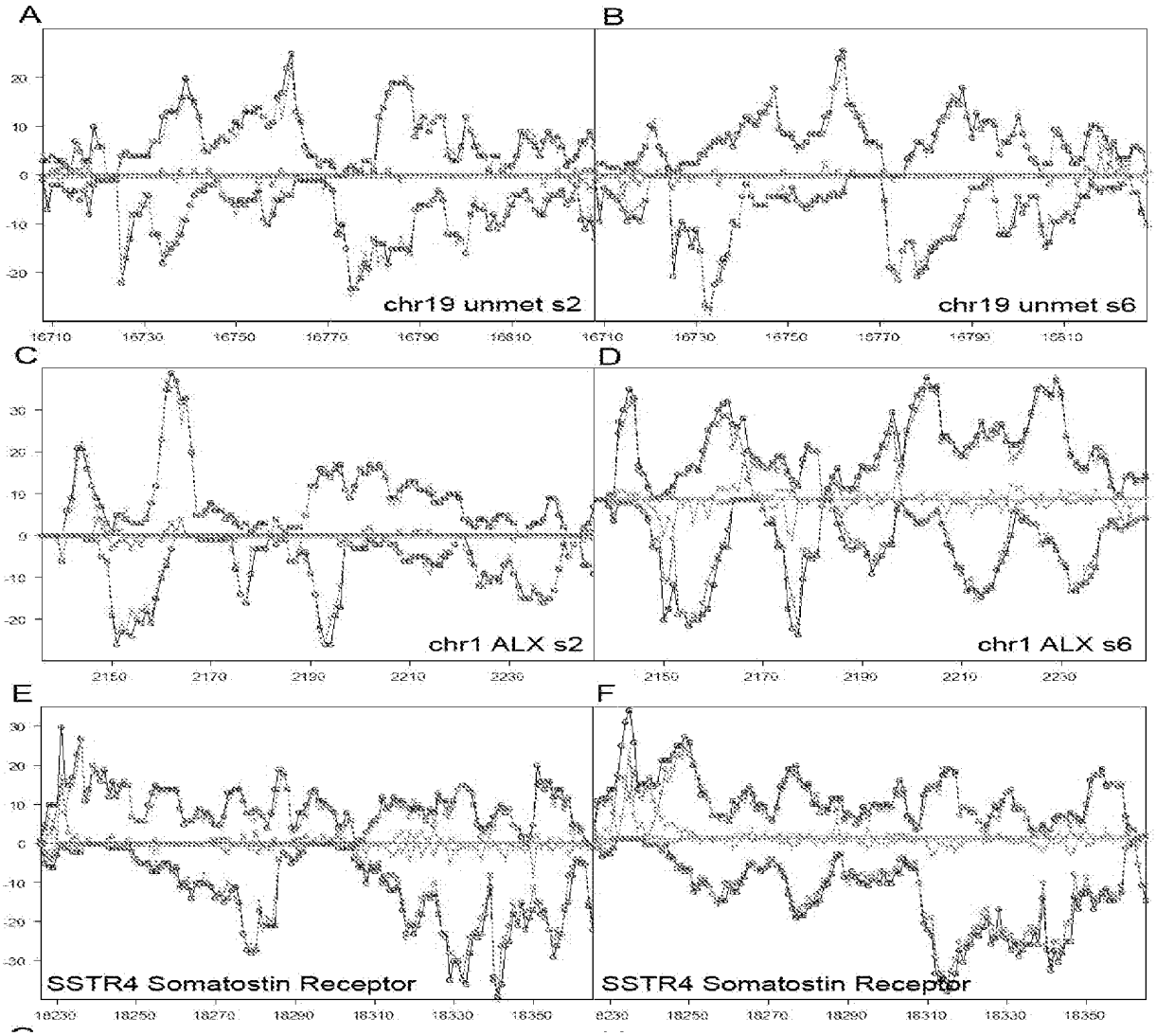

A
B
chr19 unmet s2
chr19 unmet s6
C
D
chr1 ALX s2
chr1 ALX s6
E
F
SSTR4 Somatostin Receptor
SSTR4 Somatostin Receptor

Fig. 3

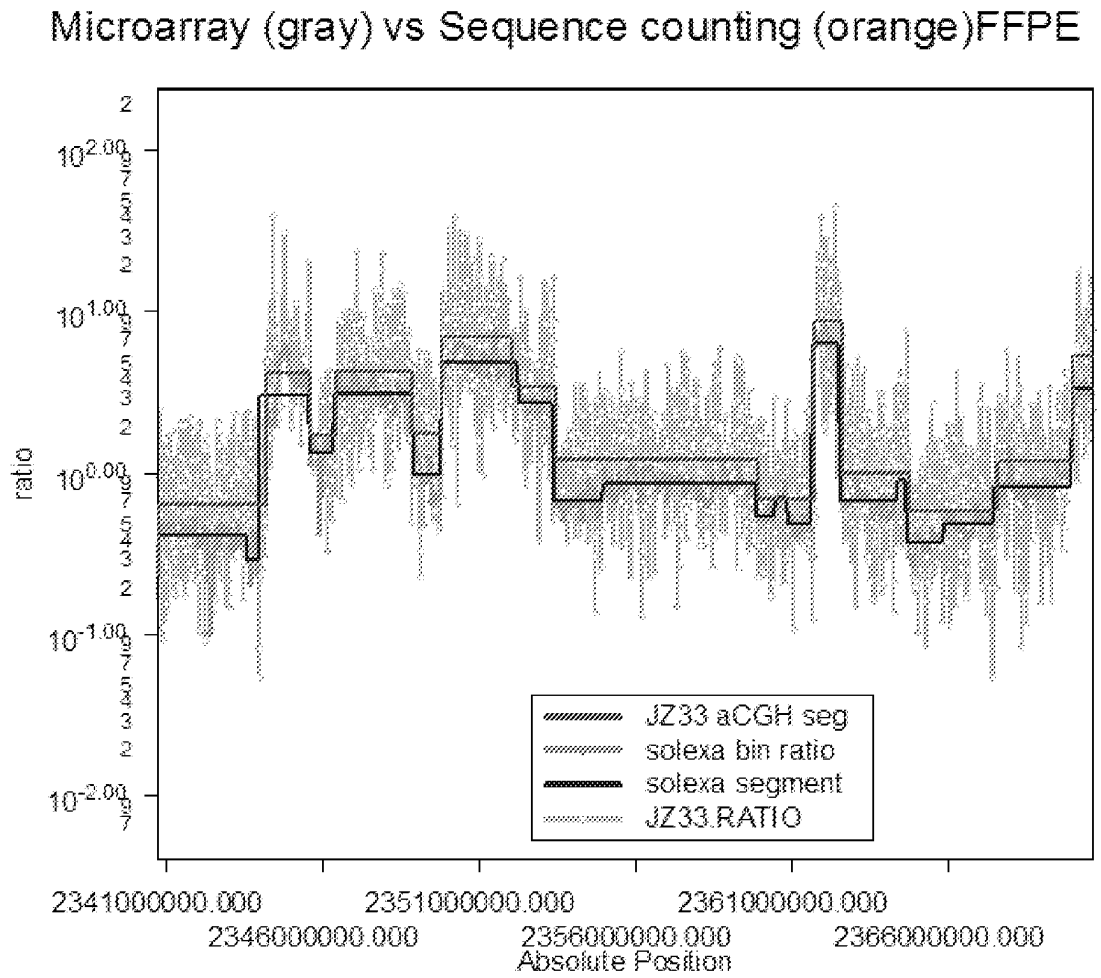


Fig. 4

IPR2025-01353
CSHL EX2001

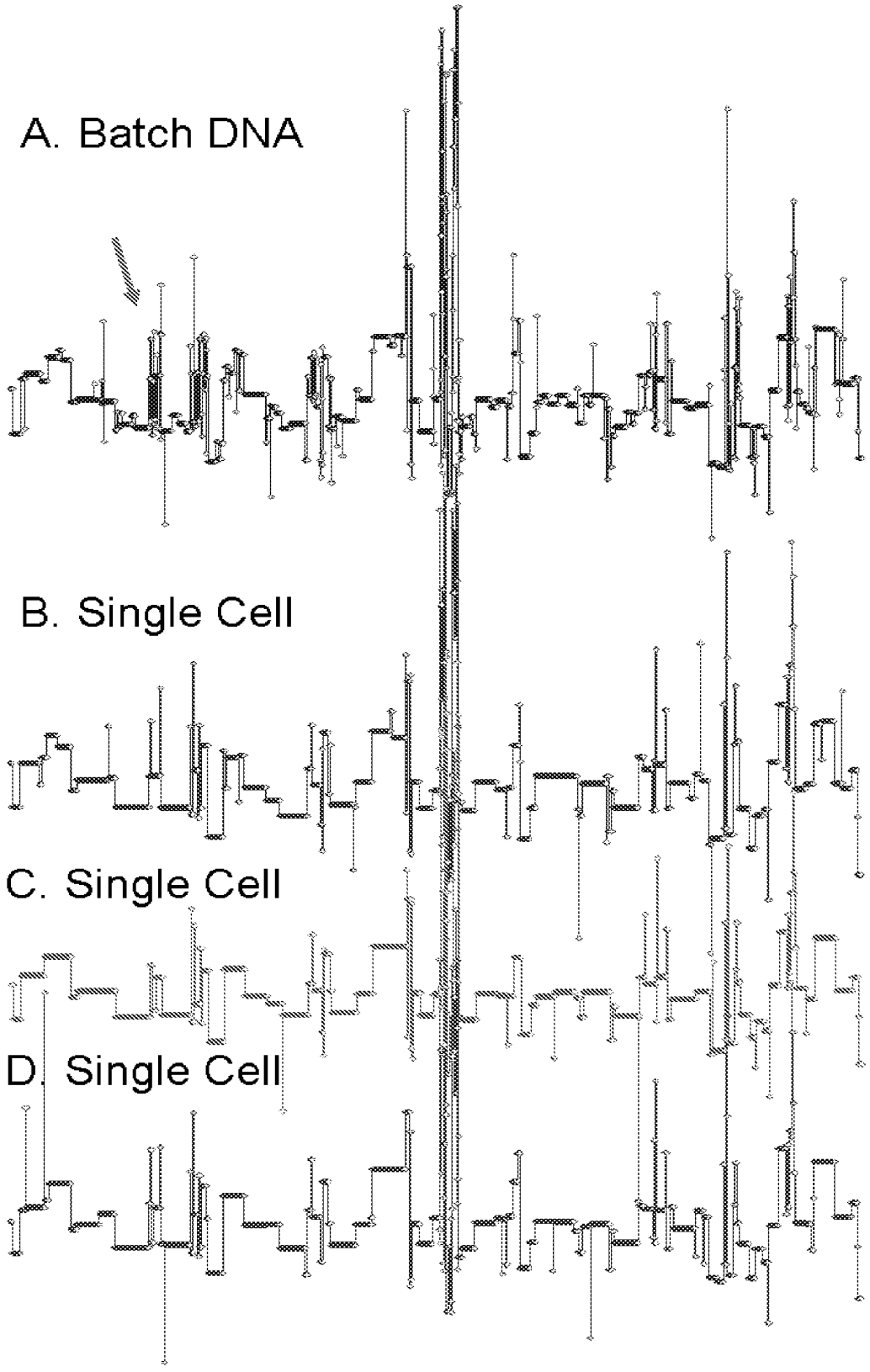


Fig. 5

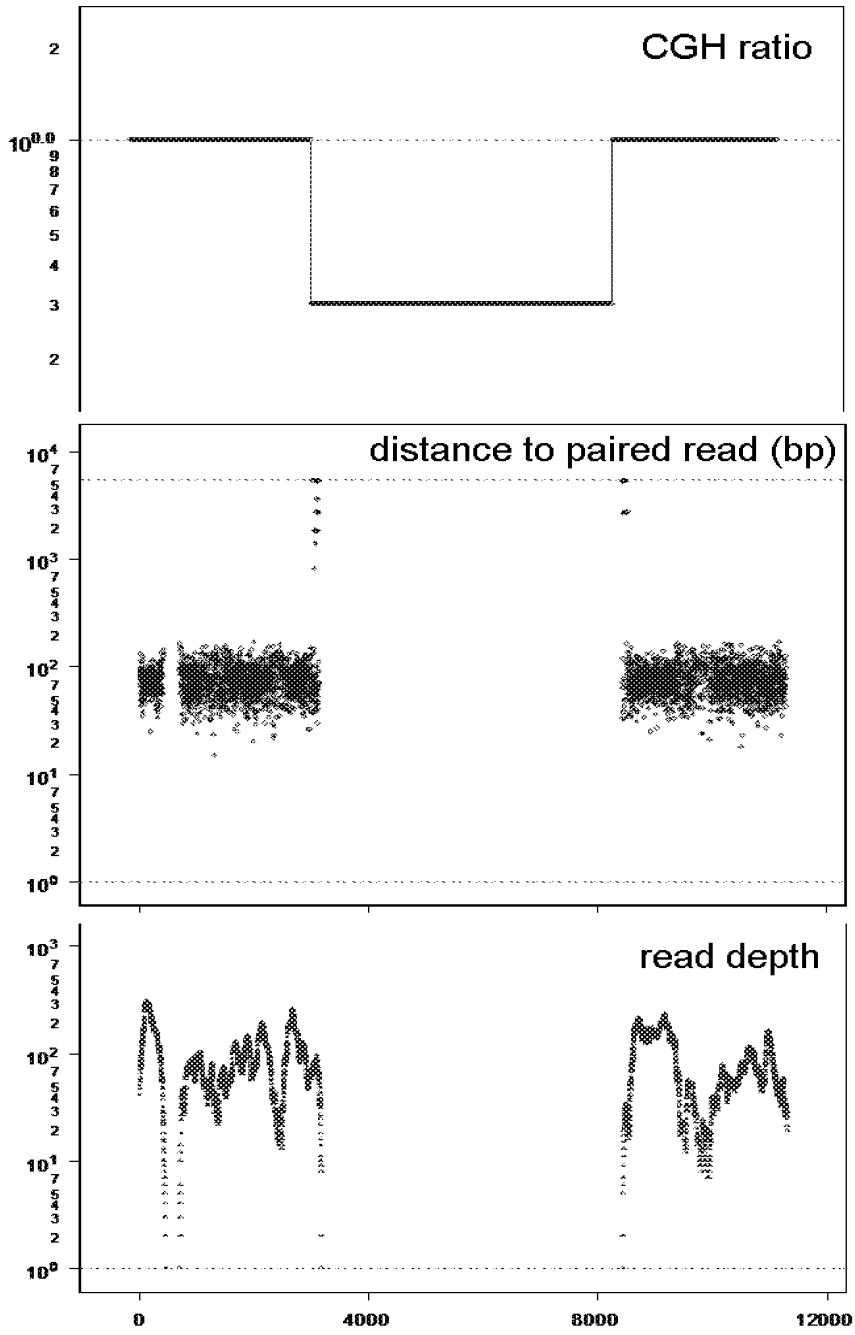

CGH ratio
distance to paired read (bp)
read depth
0
4000
8000
12000

Fig. 6

Fig. 7A

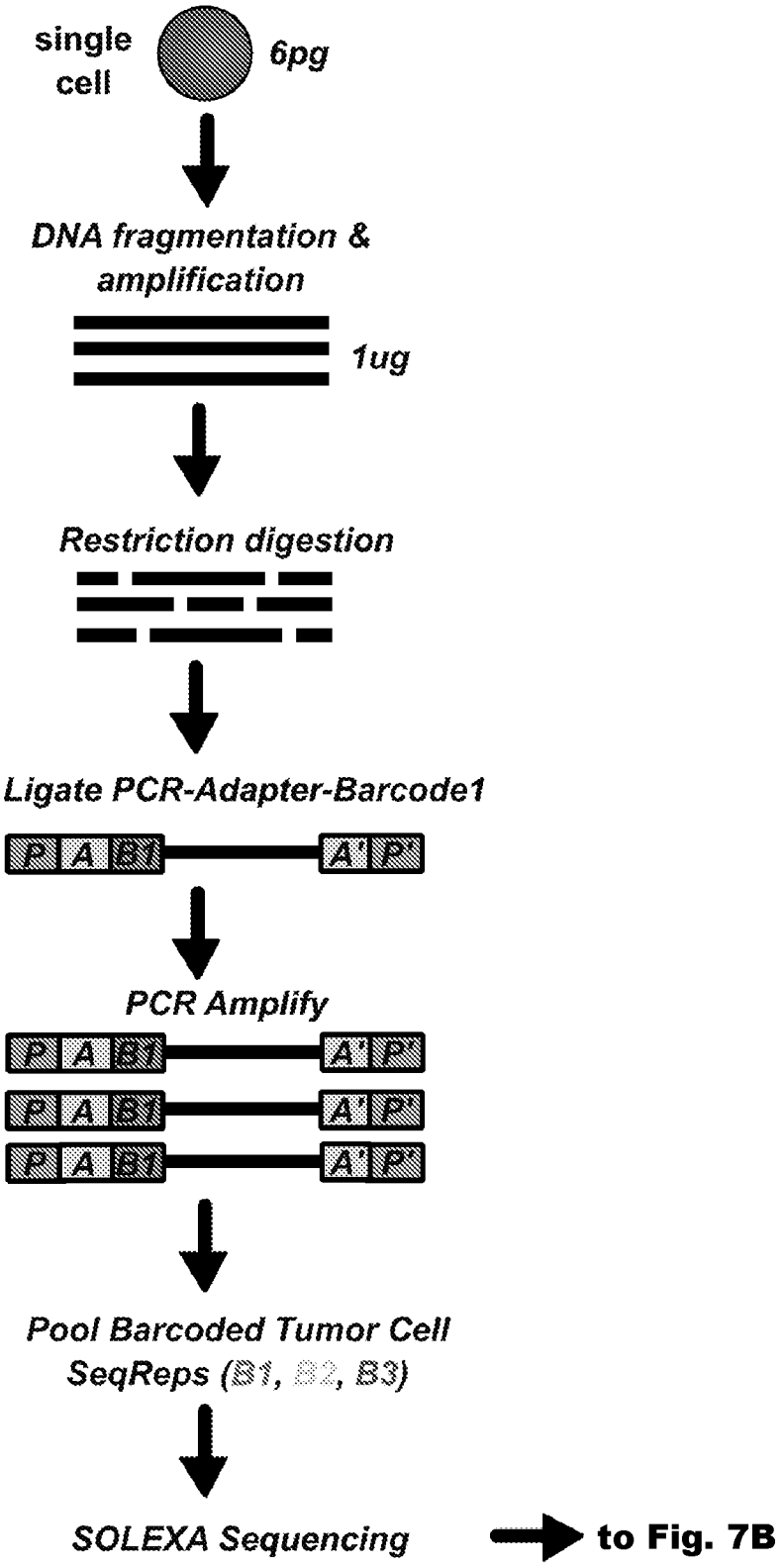
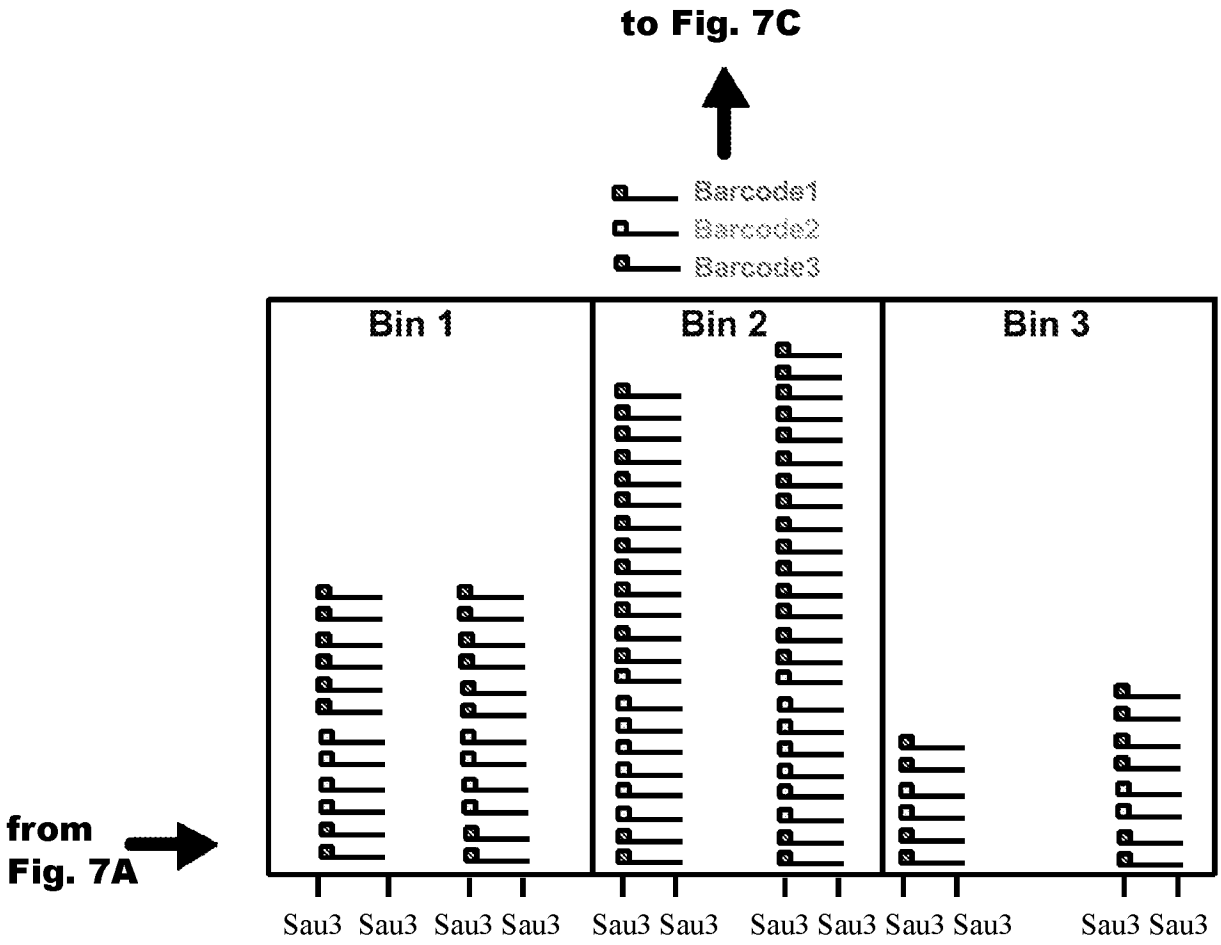
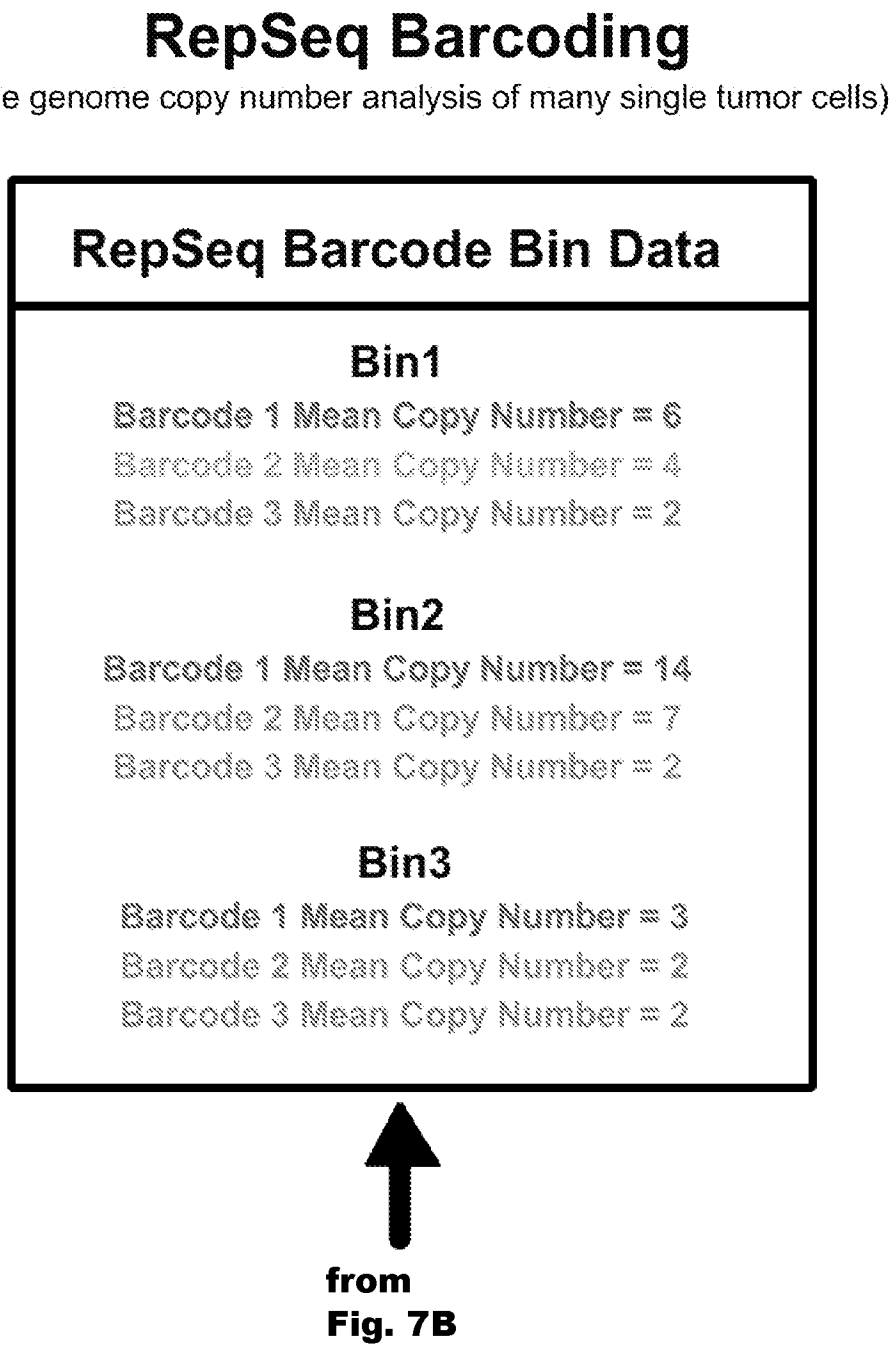

single cell
6pg
DNA fragmentation & amplification
1ug
Restriction digestion
Ligate PCR-Adapter-Barcode1
P
A
B1
A1
P1
PCR Amplify
Pool Barcoded Tumor Cell SeqReps (B1, B2, B3)
SOLEXA Sequencing
to Fig. 7B

Fig. 7B (continued from Fig. 7A)



Chromosome 17q12

Fig. 7C (continued from Fig. 7B)



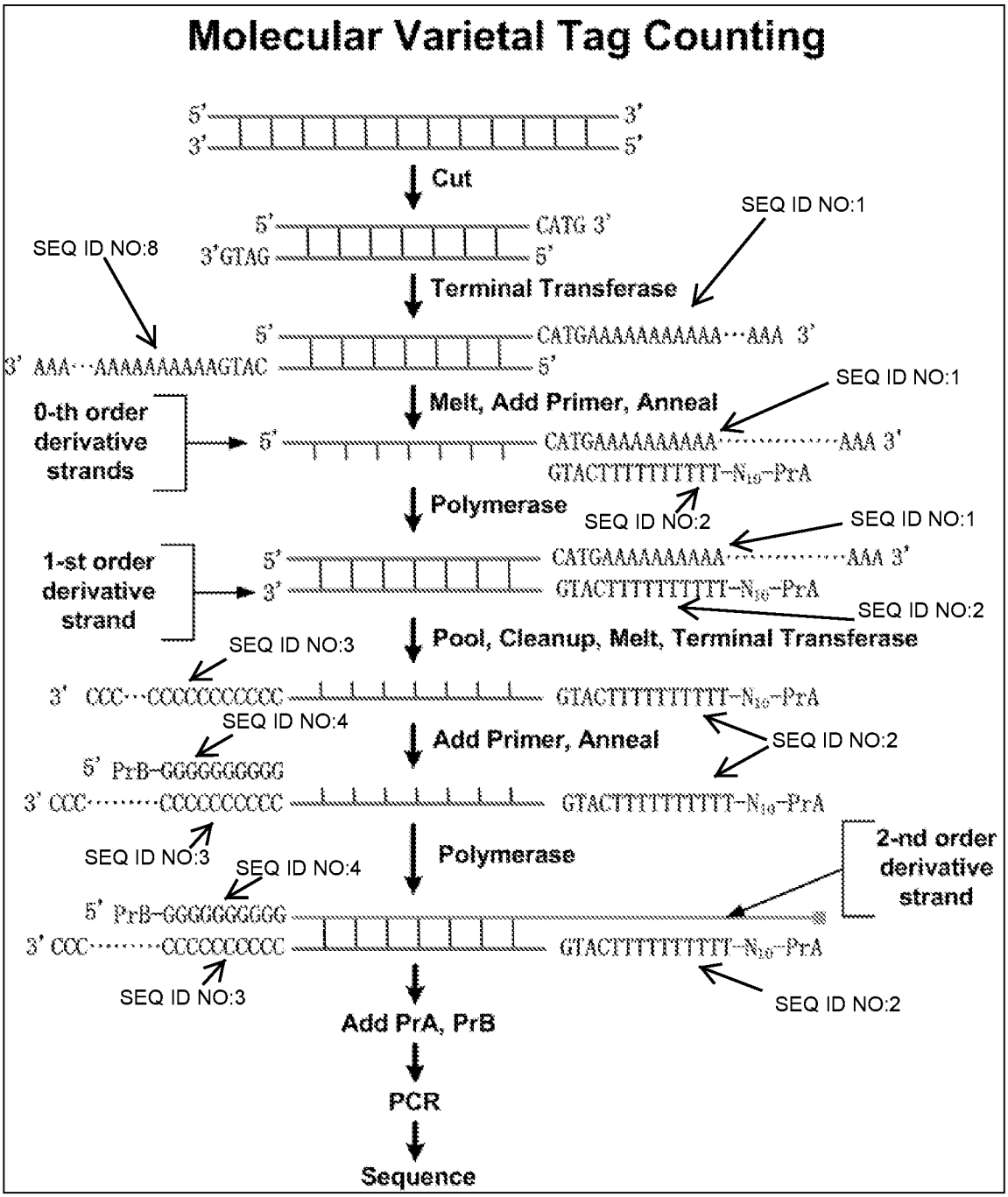
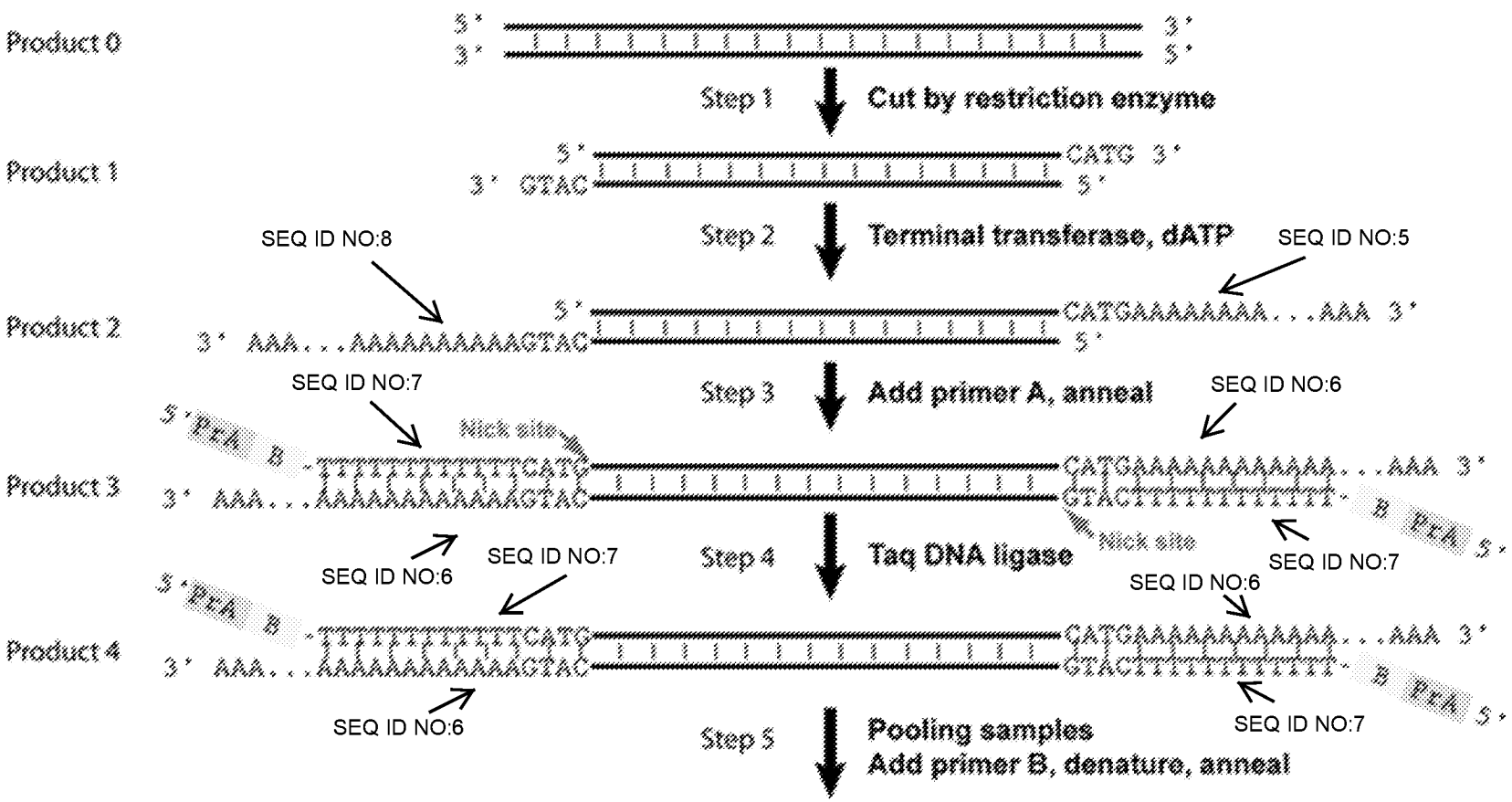

Molecular Varietal Tag Counting
Cut
SEQ ID NO:1
SEQ ID NO:8
Terminal Transferase
Melt, Add Primer, Anneal
0-th order derivative strands
SEQ ID NO:1
Polymerase
SEQ ID NO:2
SEQ ID NO:1
1-st order derivative strand
SEQ ID NO:2
SEQ ID NO:3
Pool, Cleanup, Melt, Terminal Transferase
SEQ ID NO:4
Add Primer, Anneal
SEQ ID NO:2
SEQ ID NO:3
SEQ ID NO:4
Polymerase
2-nd order derivative strand
SEQ ID NO:3
SEQ ID NO:2
Add PrA, PrB
PCR
Sequence

Fig. 8

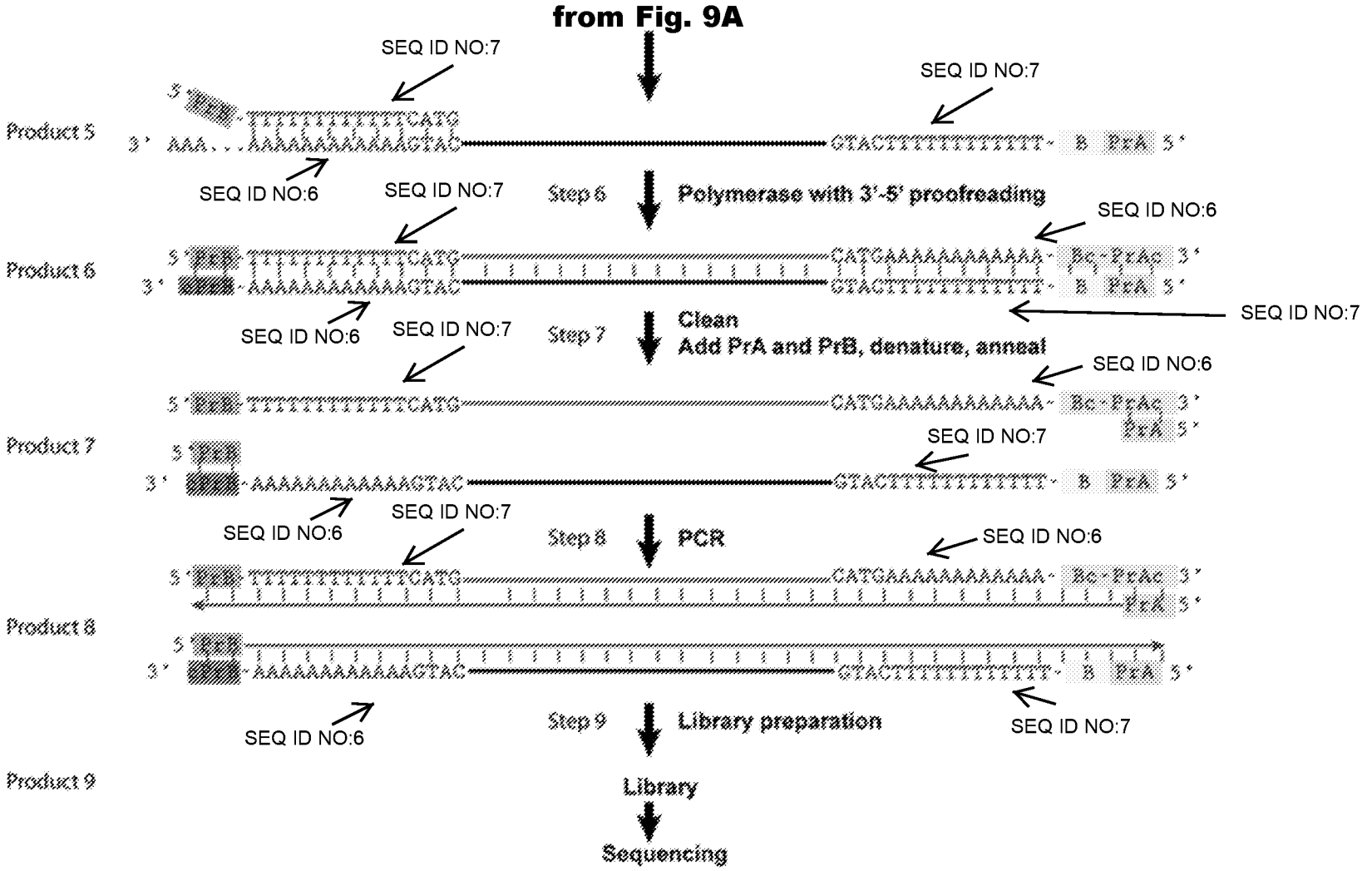
Fig. 9A



to Fig. 9B

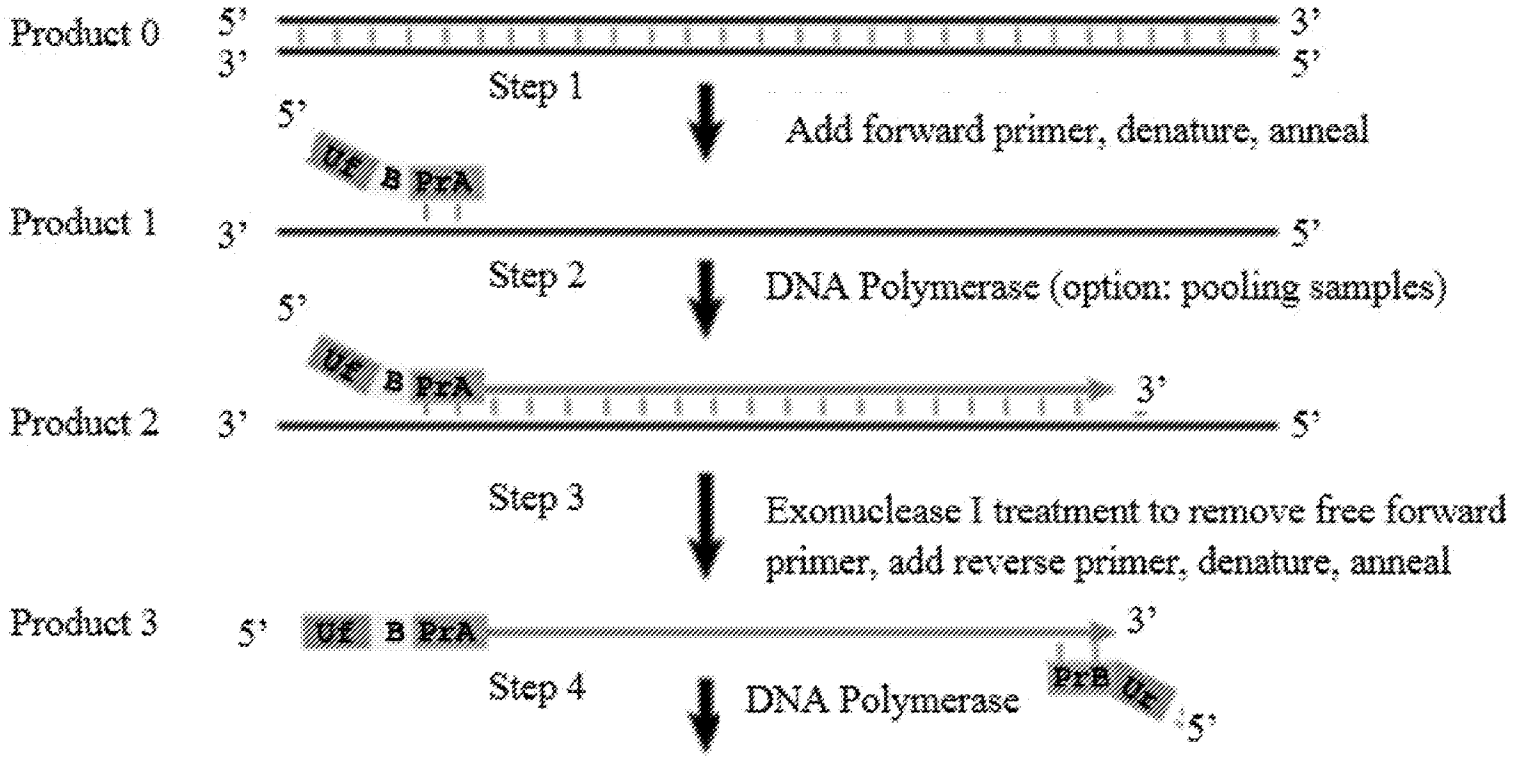
IPR2025-01353
CSHL EX2001

Fig. 9B (continued from Fig. 9A)



IPR2025-01353
CSHL EX2001

Fig. 10A

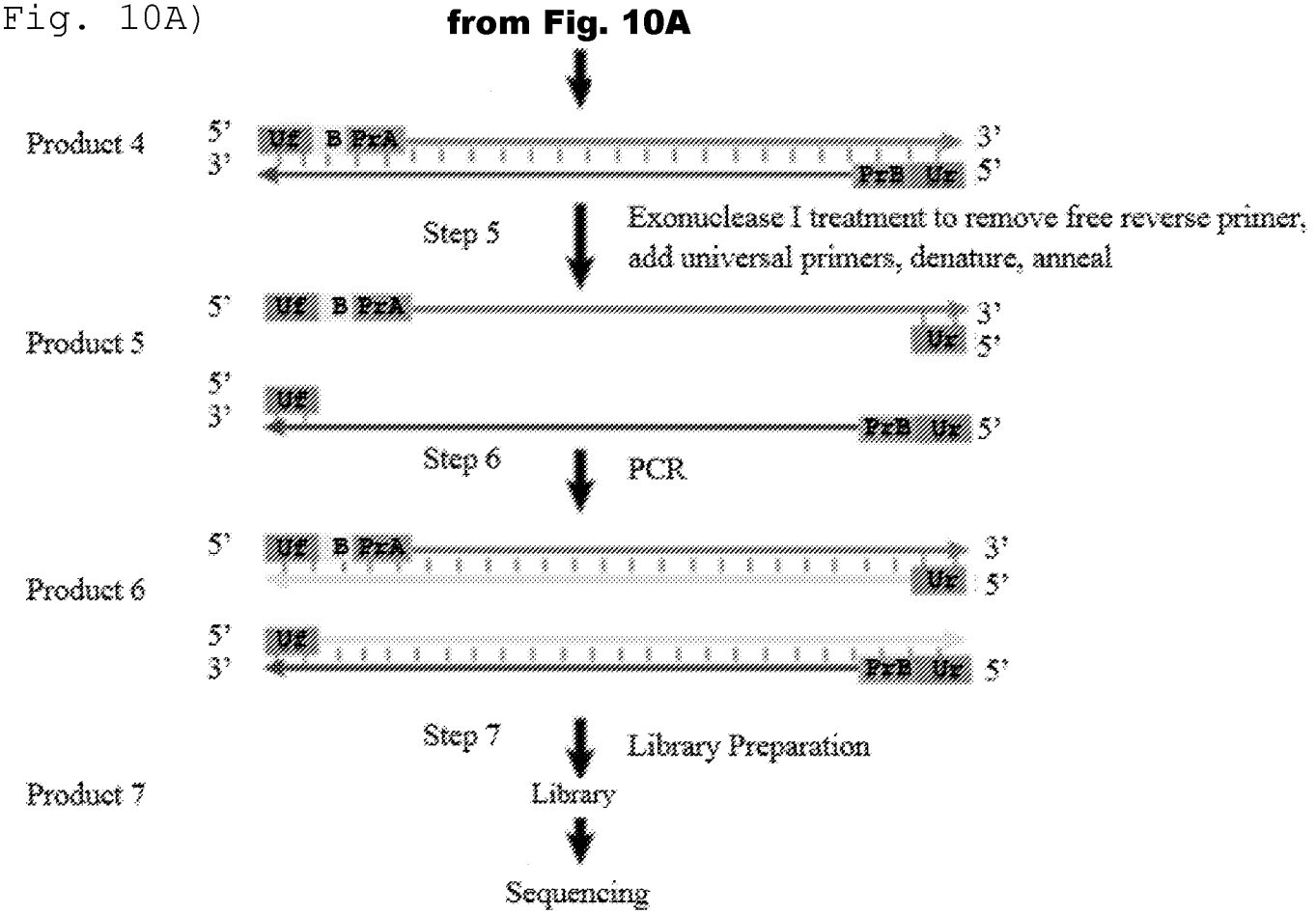


to Fig. 10B

IPR2025-01353
CSHL EX2001

Fig. 10B

(continued from Fig. 10A)



IPR2025-01353
CSHL EX2001

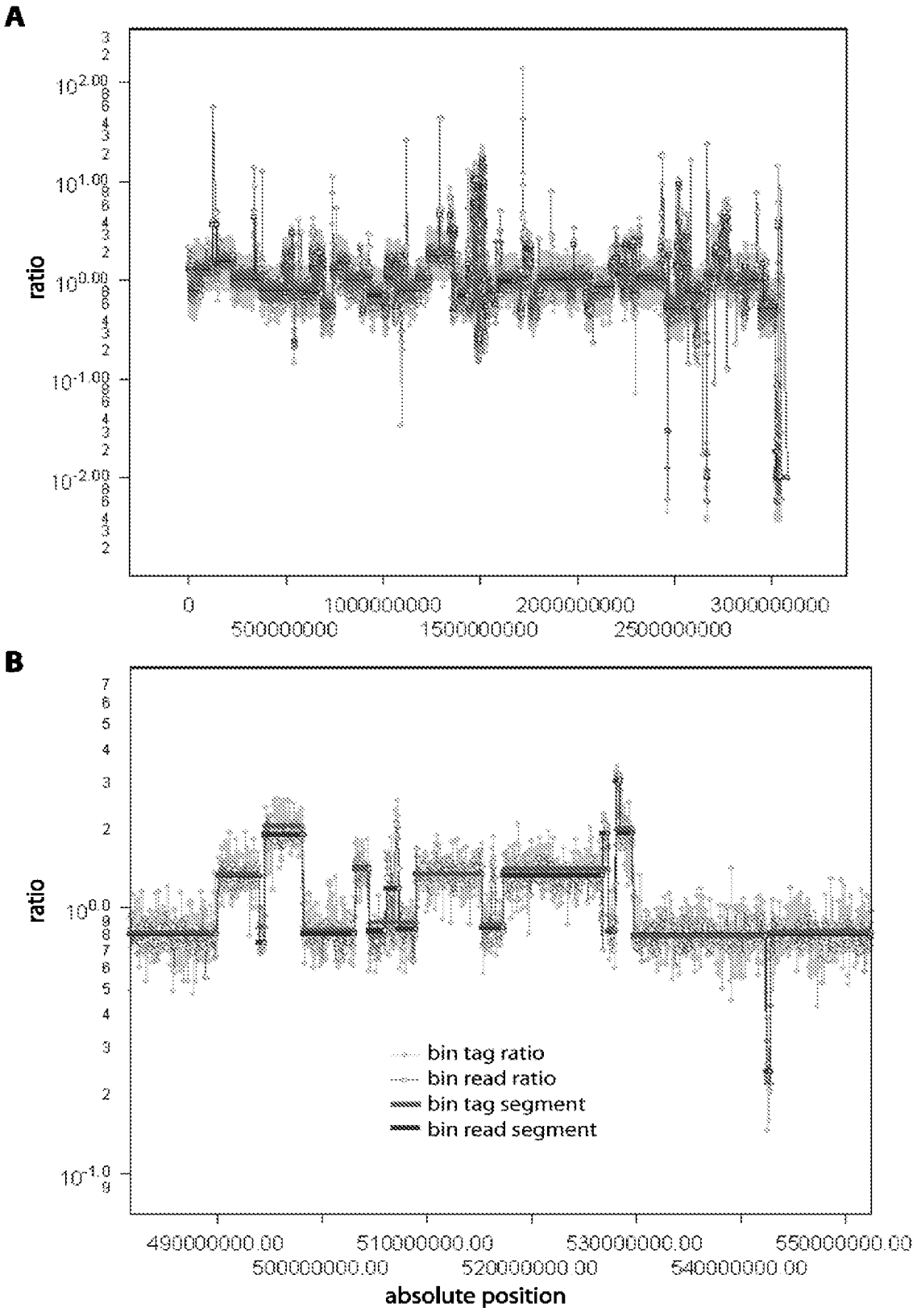

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bin read ratio
bin tag segment
bin read segment
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500000000.00
510000000.00
520000000.00
530000000.00
540000000.00
550000000.00
absolute position

Fig. 11

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	James Hicks et al.
U.S. Serial No.	:	Not Yet Known Examiner: Not Yet Assigned
Filing Date	:	Herewith Art Unit: Not Yet Assigned
Confirmation No.	:	Not Yet Known
For	:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

30 Rockefeller Plaza
20th Floor
New York, New York 10112
February 7, 2019

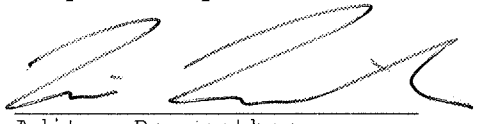
BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

STATEMENT OF COMPLIANCE UNDER 37 C.F.R. § 1.821(e)
IN CONNECTION WITH ABOVE-IDENTIFIED APPLICATION

Pursuant to 37 C.F.R. § 1.821(e), I hereby certify that the content of the Sequence Listing submitted herewith as a text file named "190207_81503-AAA_Sequence_Listing_ADR" is identical to the written sequence listing and does not introduce any new matter into the subject application.

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 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.

Respectfully submitted,



Aditya Ramanathan
/o Cooper & Dunham LLP
30 Rockefeller Plaza, 20th Fl.
New York, New York 10112
Attn.: Gary J. Gershik
(212) 278-0400

What is claimed is:

1. A method for obtaining from genomic material genomic copy number information unaffected by amplification distortion, comprising:

a) obtaining segments of the genomic material;

b) tagging the segments with substantially unique tags to generate tagged nucleic acid molecules, such that each tagged nucleic acid molecule comprises one segment of the genomic material from step (a) and a tag;

c) subjecting the tagged nucleic acid molecules to amplification by polymerase chain reaction (PCR);

d) generating tag associated sequence reads by sequencing the product of step (c);

e) assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding to a segment of the genomic material to a location on the genome; and

f) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the genome,

thereby obtaining genomic copy number information unaffected by amplification distortion.

2. The method of claim 1, further comprising estimating a genomic copy number of a region of the genome comprising more than one location on the genome by assigning as the copy number of the region the highest count obtained in step (f) for the locations within the region.

3. The method of claim 1, further comprising comparing a count obtained in step (f) for a location on the genome to a count for the same location obtained from a reference sample, thereby estimating a relative genomic copy number of the location.

4. The method of claim 1, further comprising

a) summing the counts obtained in step (f) for locations on the genome which comprise a first region of the genome, wherein the first region comprises more than one location;

b) summing the counts obtained in step (f) for locations on the genome which comprise a second region of the genome, wherein the second region is comprised of a number of locations which is comparable to the number of locations of the first region;

c) comparing the value obtained in step (a) to the value obtained in step (b),

thereby estimating the relative genomic copy number of the first region of the genome to the genomic copy number of the second region of the genome.

5. The method of claim 4, wherein step (b) further comprises

i) summing the counts obtained in step (f) for locations on the genome which comprise

a third region of the genome, wherein the third region is comprised of a number of locations which is comparable to the number of locations of the first region; and

ii) obtaining an average of the sum of the counts obtained in step (f) for locations which comprise the second region and the sum of the counts obtained in step (f) for locations which comprise the third region.

6. The method of any one of claims 4-5, wherein the second region of the genome comprises a centromere.

7. The method of claim 1, further comprising summing the counts obtained in step (f) for locations which comprise a region of the genome, and comparing the sum to a sum obtained from a reference sample for the same region of the genome, thereby estimating a relative genomic copy number of the region of the genome.

8. A method for obtaining from mRNA transcripts mRNA copy number information unaffected by amplification distortion, comprising:

a) obtaining cDNA from the mRNA transcripts;

b) optionally obtaining segments of the cDNA;

c) tagging the cDNA or segments of cDNA with substantially unique tags to generate tagged nucleic acid molecules, such that each tagged nucleic acid molecule comprises

i) one cDNA from step (a) or one segment of the cDNA from step (b), and

ii) a tag;

d) subjecting the tagged nucleic acid molecules to amplification by polymerase chain reaction (PCR);

e) generating tag associated sequence reads by sequencing the product of step (d);

f) assigning each tagged nucleic acid molecule to a location on a cDNA library associated with the mRNA transcripts by mapping the subsequence of each tag associated sequence read corresponding to a cDNA or a segment of cDNA to a location on the cDNA library; and

g) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the cDNA library,

thereby obtaining mRNA copy number information unaffected by amplification distortion.

9. A method for obtaining from mRNA transcripts mRNA copy number information unaffected by amplification distortion, comprising:

a) generating tagged nucleic acid molecules, comprising:

i) subjecting the mRNA transcripts to a polymerase reaction in the presence of primers capable of hybridizing to the polyA tail of the mRNA transcripts under

conditions that promote the formation of only one complement, thereby generating first order derivative strands;

ii) adding a polynucleotide tail to the first order derivative strands; and

iii) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (ii) under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (i) and (iii) comprise substantially unique primers, thereby generating tagged nucleic acid molecules;

b) subjecting the tagged nucleic acid molecules to polymerase chain reaction (PCR) amplification;

c) generating tag associated sequence reads by sequencing the product of step (b);

d) assigning each tagged nucleic acid molecule to a location on a cDNA library associated with the mRNA transcripts by mapping the subsequence of each tag associated sequence read corresponding to a mRNA transcript to a location on the cDNA library; and

e) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the cDNA library,

thereby obtaining mRNA copy number information unaffected by amplification distortion.

10. A method for obtaining from genomic material DNA methylation information unaffected by amplification distortion, comprising:

a) obtaining segments of the genomic material;

b) adding a polynucleotide tail to the ends of the segments of the genomic material to generate zero-th order derivative strands;

c) subjecting the zero-th order derivative strands to a polymerase reaction in the presence essentially unique primers, wherein the essentially unique primers are capable of hybridizing to the polynucleotide tail of the zero-th order strands, under conditions that promote the formation of only one complement, thereby generating tagged nucleic acid molecules;

d) separating the tagged nucleic acid molecules into a group consisting of hemi-methylated tagged nucleic acid molecules and a group consisting of unmethylated tagged nucleic acid molecules;

e) subjecting each group of step (d) to amplification by polymerase chain reaction (PCR);

f) generating tag associated sequence reads by sequencing the product of step (e);

g) assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding to a segment of the genomic material to a location on the genome; and

h) counting the number of tagged nucleic acid molecules having a different tag that have been assigned to the same location on the genome,

thereby obtaining DNA methylation information unaffected by amplification distortion.

11. The method of any one of claims 1-7, wherein tagging the segments to generate tagged nucleic acid molecules comprises:

a) adding a polynucleotide tail to the ends of the segments of the genomic material to generate zero-th order derivative strands;

b) subjecting the zero-th order derivative strands of step (a) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

c) adding a polynucleotide tail to the first order derivative strands;

d) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the

polynucleotide tail of the first order derivative strands under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (b) and (d) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

12. The method of any one of claims 1-7, wherein tagging the segments to generate tagged nucleic acid molecules comprises:

a) adding a polynucleotide tail to the ends of the segments of genomic material to generate zero-th order derivative strands,

b) subjecting the zero-th order derivative strands of step (a) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (a) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

c) subjecting the product of step (b) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (a) under conditions which promote the formation of only one complement, wherein the primers of step (c) have different nucleotide sequences than the primers of step (b), and wherein the polymerase has 3′-5′ proofreading activity,

wherein the primers of at least one of steps (b) and (c) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

13. The method of any one of claims 9-12, wherein adding a polynucleotide tail comprises the use of a terminal transferase.

14. The method of any one of claims 1-7, wherein tagging the segments to generate tagged nucleic acid molecules comprises ligation of adaptors comprising the tags to at least one end of the segments of the genomic material.

15. The method of claim 14, wherein the adaptors comprising the tags are ligated to only one end of the segments of the genomic material.

16. The method of any one of claims 1-15, wherein the tags comprise a sequence that aids PCR amplification.

17. The method of any one of claims 1-16, wherein each tagged nucleic acid molecule comprises one tag.

18. The method of any one of claims 1-17, wherein each tagged nucleic acid molecule comprises more than one tag.

19. The method of any one of claims 1-7 or 10-18, wherein segments of the genomic material are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication.

20. The method of claim 8, wherein segments of the cDNA are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication.

21. The method of any one of claims 8-9, 13, 17-18 or 20, wherein the maximum copy number of a location on a cDNA library is not less than the number of tagged nucleic

acid molecules having a different tag that have been assigned to the same location on the cDNA library.

22. The method of any one of claims 1-7 or 10-19, further comprising analyzing mRNA copy number.

23. The method of any one of claims 10, 13, 16-19, or 22, wherein separating the tagged nucleic acid molecules into a group consisting of hemi-methylated tagged nucleic acid molecules and a group consisting of unmethylated tagged nucleic acid molecules is by cleavage with methylation sensitive restriction enzymes, partitioning with antibodies, or partitioning with methyl-C binding proteins directed to methylated or hydroxymethylated cytosine.

24. The method of any one of claims 1-23, wherein the tagged nucleic acid molecules are subject to hybrid capture prior to PCR or prior to sequencing.

25. The method of any one of claims 1-24, wherein each tagged nucleic acid molecule differs at more than one nucleotide.

26. The method of any one of claims 1-25, wherein the tag sequences further comprise a sample tag.

27. The method of claim 26, wherein the tagged nucleic acid molecules are pooled with a plurality of tagged nucleic acid molecules having a different sample tag prior to PCR amplification or prior to sequencing.

28. The method of claim 27, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads according to sample tag.

29. The method of any one of claims 1-28, wherein the tagged nucleic acid molecules are generated from a single species.

30. The method of claim 29, wherein the tagged nucleic acid molecules are generated from a single organism.

31. The method of any one of claims 1-30, wherein tagged nucleic acid molecules are generated from a single cell.

32. The method of claim 31, wherein the single cell is from a needle aspirate of suspected cancer lesions.

33. The method of claim 31, wherein the single cell is from a core biopsy of suspected cancer lesions.

34. The method of claim 29, wherein the tagged nucleic acid molecules are generated from two or more organisms.

35. The method of claim 34, wherein the tagged nucleic acid molecules are generated from a single cell of each organism.

36. The method of any one of claims 30-35, wherein the single species is human.

37. The method of any one of claims 1-28, wherein the tagged nucleic acid molecules are generated from two or more species.

38. The method of claim 37, wherein the tagged nucleic acid molecules are generated from a population of microbes.

39. The method of claim 38, comprising comparing the genomic copy number information obtained for different species of the population to determine the relative count of those different species in the population.

40. A composition of matter derived from genomic material comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining segments of the genomic material;

b) adding a polynucleotide tail to the ends of the segments of the genomic material to generate zero-th order derivative strands;

c) subjecting the zero-th order derivative strands of step (b) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

d) adding a polynucleotide tail to the first order derivative strands;

e) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the first order derivative strands under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (c) and (e) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

41. A composition of matter derived from genomic material comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining segments of genomic material;

b) adding a polynucleotide tail to the ends of the segments of genomic material to generate zero-th order derivative strands,

c) subjecting the zero-th order derivative strands of step (b) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (b) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

d) subjecting the product of step (c) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (b) under conditions which promote the formation of only one complement, wherein the primers of step (d) have different nucleotide sequences than the primers of step (c), and wherein the polymerase has 3′-5′ proofreading activity,

wherein the primers of at least one of steps (c) and (d) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

42. A composition of matter derived from mRNA transcripts comprising tagged nucleic acid molecules, said tagged

nucleic acid molecules being produced by a process comprising:

a) obtaining cDNA from the mRNA transcripts;

b) optionally obtaining segments of the cDNA; and

c) tagging the cDNA or segments of cDNA with substantially unique tags to generate tagged nucleic acid molecules, wherein each tagged nucleic acid molecule comprises

iii) one cDNA from step (a) or one segment of the cDNA from step (b) and

iv) a tag.

43. A composition of matter derived from mRNA transcripts comprising tagged nucleic acid molecules, said tagged nucleic acid molecules being produced by a process comprising:

a) obtaining mRNA transcripts;

b) subjecting the mRNA transcripts to a polymerase reaction in the presence of primers capable of hybridizing to the polyA tail of the mRNA transcripts under conditions that promote the formation of only one complement, thereby generating first order derivative strands;

c) adding a polynucleotide tail to the first order derivative strands;

d) subjecting the first order derivative strands to a polymerase reaction in the presence of primers capable of hybridizing to the

polynucleotide tail added in step (c) under conditions that promote the formation of only one complement, thereby generating second order derivative strands,

wherein the primers of at least one of steps (b) and d) comprise substantially unique primers, thereby generating tagged nucleic acid molecules.

44. The composition of matter of any one of claims 40-41 or 43, wherein adding a polynucleotide tail comprises the use of a terminal transferase.

45. The composition of matter of any one of claims 40-44, wherein each tagged nucleic acid molecule comprises one tag.

46. The composition of matter of any one of claims 40-44, wherein each tagged nucleic acid molecule comprises more than one tag.

47. The composition of matter of any one of claims 40-41 or 44-46, wherein segments of the genomic material are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication.

48. The composition of matter of any one of claims 42-46, wherein segments of the cDNA are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication.

49. The composition of matter of any one of claims 40-48, wherein the complexity of the tagged nucleic acid molecules is reduced by hybrid capture.

50. The composition of matter of any one of claims 40-49, wherein each tagged nucleic acid molecules differs at more than one nucleotide.

51. The composition of matter of any one of claims 40-50, wherein the tag sequences further comprise a sample tag.

52. A composition of matter comprising at least two pools of tagged nucleic acid molecules according to claim 51.

53. The composition of matter of any one of claims 40-52, wherein the tagged nucleic acid molecules are generated from a single cell.

54. The composition of matter of claim 53, wherein the single cell is from a needle aspirate of suspected cancer lesions.

55. The composition of matter of claim 53, wherein the single cell is from a core biopsy of suspected cancer legions.

56. The composition of matter of any one of claims 40-52, wherein the tagged nucleic acid molecules are generated from two or more organisms.

57. A kit for determining nucleic acid copy number information unaffected by amplification distortion comprising:

a) a terminal transferase, and

b) plurality of substantially unique primers,

wherein the substantially unique primers comprise substantially unique tags, and wherein the substantially unique primers are capable of hybridizing to the polynucleotide tail of a nucleic acid molecule which has a polynucleotide tail added by the terminal transferase.

58. The kit of claim 57, further comprising a DNA polymerase having 3′-5′ proofreading activity.

59. The kit of any one of claims 57-58, wherein the plurality of substantially unique primers comprises 10^n primers, wherein n is an integer from 2 to 9.

60. The kit of any one of claims 57-59, further comprising a second terminal transferase and a primer capable of hybridizing to the polynucleotide tail of a nucleic acid molecule which has a polynucleotide tail added by the second terminal transferase.

61. The kit of any one of claims 57-60, wherein the tags are six nucleotides long.

62. The kit of any one of claims 57-60, wherein the tags are 15 nucleotides long.

63. The kit of any one of claims 57-62, further comprising sample tags.

64. The kit of claim 63, wherein the sample tags are 2 nucleotides long.

65. The kit of claim 63, wherein the sample tags are 4 nucleotides long.

66. The kit of any one of claims 63-65, wherein the sample tags comprise a sample tag set.

67. The kit of any one of claims 63-66, wherein the substantially unique tags comprise the sample tags.

5981/81503-AAA/GJG/ADR

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Abstract of the Disclosure

A method for obtaining from genomic material genomic copy number information unaffected by amplification distortion, comprising obtaining segments of the genomic material, tagging the segments with substantially unique tags to generate tagged nucleic acid molecules, such that each tagged nucleic acid molecule comprises one segment of the genomic material and a tag, subjecting the tagged nucleic acid molecules to polymerase chain reaction (PCR) amplification, generating tag associated sequence reads by sequencing the product of the PCR reaction, assigning each tagged nucleic acid molecule to a location on a genome associated with the genomic material by mapping the subsequence of each tag associated sequence read corresponding to a segment of the genomic material to a location on the genome, and counting the number of tagged nucleic acid molecules assigned to the same location on the genome having a different tag, thereby obtaining genomic copy number information unaffected by amplification distortion.

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 16269818 Document Date: 02/07/2019

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

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SCORE Placeholder Sheet for IFW Content

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The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

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- Drawing

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- External customers may access SCORE content via PAIR using the Supplemental Content tab.

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IPR2025-01353
CSHL EX2001

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/269,818

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	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	330		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	380		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 230 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	785		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.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR

CONFIRMATION NO. 8088

23432
COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

INFORMAL NOTICE

OC000000105919651

Date Mailed: 02/14/2019

INFORMATIONAL NOTICE TO APPLICANT

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

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

A new inventor's oath or declaration that identifies this application (e.g., by Application Number and filing date) is required. The inventor's oath or declaration does not comply with 37 CFR 1.63 in that it:

- does not state that the above-identified application was made or authorized to be made by the person executing the oath or declaration.

James Hicks
Nicholas Navin
Jennifer Troge
Zihua Wang
Michael Wigler

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**.

/ambalinang/

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/269,818	02/07/2019	1662	785	81503-AAA/GJG/ADR	1	1

CONFIRMATION NO. 8088

FILING RECEIPT

23432
COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

OC000000105919650

Date Mailed: 02/14/2019

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)

James Hicks, Locust Valley, NY;
Nicholas Navin, Houston, TX;
Jennifer Troge, Oyster Bay, NY;
Zihua Wang, Huntington, NY;
Michael Wigler, Cold Spring Harbor, NY;

Applicant(s)

Cold Spring Harbor Laboratory, Cold Spring Harbor, NY;

Assignment For Published Patent Application

Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 15/063,278 03/07/2016
which is a CON of 13/278,333 10/21/2011 PAT 9404156
which claims benefit of 61/510,579 07/22/2011
and claims benefit of 61/406,067 10/22/2010

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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: 02/14/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/269,818**

Projected Publication Date: 05/23/2019

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **
Title

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Preliminary Class

800

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 patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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

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

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

NOT GRANTED

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

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 03/20/2019

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
03/20/2019	PAPER

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.

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
16/269,818	02/07/2019	Hicks et al.	81503-AAA/GJG/ADR

COOPER & DUNHAM, LLP
30 Rockefeller Plaza 20th Floor
NEW YORK, NY 10112

EXAMINER	
FRANK LU	
ART UNIT	PAPER
1634	20190307

DATE MAILED: _____

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

This is a decision on the Petition to Accept Color Drawings under 37 C.F.R. § 1.84(a)(2), received in the United States Patent and Trademark Office (USPTO) on February 7, 2019.

The petition is GRANTED.

A grantable petition under 37 C.F.R. 1.84(a)(2) must meet the following requirements:
1. Payment of the fee set forth under 37 C.F.R. 1.17(h),
2. Submission of three (3) sets of color drawings, or one (1) set of color drawings if filed by EFS-Web, and
3. The first paragraph of the brief description of the drawings in the Specification, or an amendment to the Specification if it is not present in the original Specification, contains the following required language pertaining to colored drawings: The patent of application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing (s) will be provided by the office upon request and payment of the necessary fee.

A review of U.S. Patent and Trademark records indicates that each of the above three requirements have been satisfied. Accordingly, the petition under 37 C.F.R. § 1.84(a) is GRANTED.

Should there be any questions with respect to this decision, please contact:
Scarlett Goon

/SCARLETT Y GOON/ Quality Assurance Specialist, TC 1600	/ANNE M. GUSSOW/ Supervisory Patent Examiner, Art Unit 1600

PTO-90C (Rev.04-03)

Technology Center Petition Count Sheet

Application No.	Applicant(s)	
16/269,818	Hicks et al.	

Petition Code	Petition Type
☐ 601	Petition to Make Special, Age or Health (37 CFR 1.102, MPEP § 708.02)
☐ 604	Petition to Make Special, Accelerated Examination (37 CFR 1.102, MPEP § 708.02)
☐ 607	Petition to Make Special, For Reasons not Provided in 601-606 and 639-640 (37 CFR 1.102, MPEP § 708.02)
☐ 608	Petition to Reopen After a Board Decision (37 CFR 1.198)
☐ 609	Petition for Review of Final Restriction Requirement (37 CFR 1.144)
☐ 610	Petition Invoking Authority of Commissioner under 37 CFR 1.181 Not Specified in Codes 611-617
☐ 611	Petition Relating to Prematureness of Final Rejection (37 CFR 1.181, MPEP § 706.07)
☐ 612	Petition Relating to Refusal to Enter an Amendment (37 CFR 1.181 and 1.127, MPEP § 714.09)
☐ 613	Petition Relating to Withdraw of holding of Abandonment (37 CFR 1.137, MPEP § 711.03)
☐ 614	Petition Relating to Withdraw of holding of Abandonment (37 CFR 1.137, MPEP § 7.14.19)
☐ 615	Petition Relating to Formal Sufficiency / Propriety of Affidavits (37 CFR 1.131, 1.132, 1.608, MPEP § 608.04(C)
☐ 617	Petition Relating to Refusal to Enter an Amendment (37 CFR 1.312)
☐ 620	Petition for Extension of Time (37 CFR 1.136 (b))
☐ 622	Petition Concerning Appeal Application before Transfer of Jurisdiction to Board of Appeals (MPEP § 1206)
☐ 623	Petition for Second or Subsequent Suspension of Action (37 CFR 1.103, MPEP § 709)
☐ 634	Petition to Correct Inventorship in a Patent not in Interference (37 CFR 1.324, MPEP § 1481)
☐ 635	Petition to Correct Inventorship in a Patent Application (37 CFR 1.48)
☐ 636	Petition to Change Inventorship in a Patent (37 CFR 1.324)
☐ 637	Petition to Withdraw from Issue, before Payment of an Issue Fee (37 CFR 1.313(a))
☐ 639	Petition for Make Special Prospective Manufacture (37 CFR 1.102, MPEP § 708.02)
☐ 646	Petition for Make Special Accelerated Examination
☑ 690	Petition Related Color Drawings of Photographs
☐ 699	Petition for Matters Before Technology Center

Information Required for OPESS Processing

☑ GRANTED ☐ GRANTED-IN-PART ☐ DENIED ☐ DISMISSED

☑ Mail Decision and Enter Decision in Petition Database/PALM
☐ Copy Decision, Send to Scanning
☐ Fees Need to be Charged
☐ _____

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/269,818	Filing Date 02/07/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	04/19/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 20	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)		(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 $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.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/DEIDRE C KING-WOODWARD/
*** 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: James Hicks et al.		
U.S. Serial No.	: 16/269,818	Examiner:	Not Yet Assigned
Filing Date	: February 7, 2019	Art Unit:	Not Yet Assigned
Conf. No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

30 Rockefeller Plaza
20th Floor
New York, New York 10112
April 19, 2019

BY EFS
Commissioner for Patents
Alexandria, VA

FIRST INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. § 1.56, applicant directs the Examiner's attention to the following documents which are listed on Form PTO-1449 **(Exhibit A)** and are also listed below.

This Information Disclosure Statement is being submitted before the mailing of the first Office Action on the merits. Thus, no fee is required, and this Information Disclosure Statement should be entered and considered.

The above-identified application claims benefit under 35 U.S.C. §120 of U.S. Serial No. 13/278,333, filed October 21, 2011, now U.S. Patent No. 9,404,156, issued August 2, 2016, and U.S. Serial No. 15/063,278, filed March 7, 2016, published as U.S. Patent Application Publication No. 2016-0251715 on September 1, 2016. U.S. Serial No. 13/278,333, issued as U.S. Patent No. 9,404,156, from which the above-identified application claims benefit is listed hereinunder as reference **4**. U.S. Serial No. 15/063,278, published as U.S. Patent Application Publication No. 2016/0251715, from which the above-identified application claims benefit is listed hereinunder as reference **19**. Applicants respectfully direct the Examiner to review the file history of each of these applications.

Counterpart PCT International Application No. PCT/US2011/057350, filed

October 21, 2011, published as PCT International Patent Application Publication No. WO 2012/054873 on April 26, 2012, is listed hereinunder as reference **38**.

Each of reference items **40-55** was issued in connection with the examination of one or more foreign counterpart applications to the instant application. Reference item **49** is a Communication of a notice of opposition issued by the European Patent Office on February 1, 2019 in connection with EP2630263. Reference item **48** is the Notice of opposition to a European Patent filed January 25, 2019 against counterpart foreign patent, European Patent No. EP2630263. Each of reference items **29, 32, 40, 59, 65, and 70** were cited in reference item **48**.

Reference items **1-37** are either U.S. Patents or U.S. Patent application publications. Pursuant to 37 C.F.R 1.98(a)(2)(ii), copies of references **1-37** are not being submitted.

Copies of references **38-75** listed below have previously been submitted to or cited by the U.S. Patent and Trademark Office in connection with U.S. Serial No. 13/278,333 or U.S. Serial No. 15/063,278. Therefore, in accordance with 37 C.F.R. §1.98(d), copies of the previously submitted or cited references are not provided.

U.S. Patents and Patent Applications

1. U.S. Patent No. 9,670,536, issued June 6, 2018 (Casbon et al.);

2. U.S. Patent No. 9,487,829 B2, issued November 8, 2016 (Vogelstein et al.);

3. U.S. Patent No. 9,476,095 B2, issued October 25, 2016 (Vogelstein et al.);

4. U.S. Patent No. 9,404,156 B2, issued August 2, 2016 (Hicks et al.);

5. U.S. Patent No. 8,741,606, issued June 3, 2014 (Casbon et al.);

6. U.S. Patent No. 8,694,263, issued April 8, 2014 (Wigler et al.);

7. U.S. Patent No. 8,663,917, issued March 4, 2014 (Wigler et al.);

8. U.S. Patent No. 8,554,488, issued October 8, 2013 (Wigler et al.);

9. U.S. Patent No. 8,273,871, issued September 25, 2012 (Hannon et al.);

10. U.S. Patent No. 7,700,324, issued April 20, 2010 (Issa et al.);

11. U.S. Patent No. 7,622,281, issued November 24, 2009 (Ronaghi et al.);

12. U.S. Patent No. 7,537,897, issued May 26, 2009 (Brenner et al.);

13. U.S. Patent No. 7,531,307, issued May 12, 2009 (Wigler et al.);

14. U.S. Patent No. 6,569,617, issued May 27, 2003 (Wigler et al.);

15. U.S. Patent No. 6,172,214, January 9, 2001 (Brenner et al.);

16. U.S. Patent No. 6,013,445, issued January 11, 2000 (Albrecht et al.);

17. U.S. Patent No. 5,639,603, issued June 17, 1997 (Dower et al.);

18. U.S. Patent Application Publication No. 2017/0051347 A1, published February 23, 2017 (Vogelstein et al.);

19. U.S. Patent Application Publication No. 2016/0251715 A1, published September 1, 2016 (Hicks et al.);

20. U.S. Patent Application Publication No. 2016/0215333 A1, published July 28, 2016 (Vogelstein et al.);

21. U.S. Patent Application Publication No. 2014/0025307, published January 23, 2014 (Wigler et al.);

22. U.S. Patent Application Publication No. 2013/0179999, published

July 11, 2013 (Hannon et al.);

23. U.S. Patent Application Publication No. 2012/0328607, published December 27, 2012 (Hicks et al.);

24. U.S. Patent Application Publication No. 2012/0149593, published June 14, 2012 (Hicks et al.);

25. U.S. Patent Application Publication No. 2010/0227768, published September 10, 2010 (Wigler et al.);

26. U.S. Patent Application Publication No. 2010/0203538, published August 12, 2010 (Dube et al.);

27. U.S. Patent Application Publication No. 2010/178655, published July 15, 2010 (Hamilton et al.);

28. U.S. Patent Application Publication No. 2009/0137402, published May 28, 2009 (Wang et al.);

29. U.S. Patent Application Publication No. 2008/0261204, published October 23, 2008 (Lexow);

30. U.S. Patent Application Publication No. 2007/0207481, published September 6, 2007 (Wigler et al.);

31. U.S. Patent Application Publication No. 2007/0172873, published July 26, 2007 (Brenner et al.);

32. U.S. Patent Application Publication No. 2007/0020640, published January 25, 2007 (McCloskey et al.);

33. U.S. Patent Application Publication No. 2006/0073506, April 6, 2006 (Christians et al.);

34. U.S. Patent Application Publication No. 2006/0035258, published February 16, 2006 (Tadakamalla et al.);

35. U.S. Patent Application Publication No. 2005/0266444, published

December 1, 2005 (Wigler et al.);

36. U.S. Patent Application Publication No. 2005/0032095, published February 10, 2005 (Wigler et al.);

37. U.S. Patent Application Publication No. 2004/110153, published June 10, 2004 (Dong et al.);

Foreign Patents, Patent Applications, and Prosecution

38. PCT International Publication No. WO 2012/054873, published April 26, 2012 to Hicks et al.;

39. PCT International Publication No. WO 2007/062445, published June 7, 2007 to Alexander Seitz;

40. English Translation of German Patent Publication No. DE 10 2008 025 656 A1, published December 3, 2009 (Björn Rotter);

41. June 26, 2012 International Search Report issued in connection with PCT International Application No. PCT/US2011/057350 (WO 2012/054873);

42. April 23, 2013 International Preliminary Report on Patentability issued in connection with PCT International Application No. PCT/US2011/057350 (WO 2012/054873);

43. February 13, 2014 Extended European Search Report, issued in connection with European Patent Application No. 11835243.4;

44. November 20, 2015 Communication under Rule 94(3) EPC issued by the European Patent Office in connection with European Patent Application No. 11835243.4;

45. June 27, 2016 Amendment under Rule 94(3) EPC to November 20, 2015 Communication under Rule 94(3) EPC issued by the European Patent Office in connection with European Patent Application No. 11835243.4;

46. October 9, 2017 Communication under Rule 71(3) EPC issued by the European Patent Office in connection with European Patent Application No. 11835243.4;

47. February 16, 2018 Amendment under Rule 71(3) EPC to October 9, 2017 Communication under Rule 71(3) EPC issued by the European Patent Office in connection with European Patent Application No. 11835243.4;

48. Notice of Opposition to a European Patent, filed January 25, 2019 by Opponent, James Poole Limited, with European Patent Office, concerning European Patent No. EP 2630263;

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50. December 8, 2017 Office Action issued by the Canadian Intellectual Property Office in connection with Canadian Patent Application 2,815,076;

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54. May 2, 2017 Response to April 20, 2017 Patent Examination Report No. 2 issued by IP Australia in connection with Australian Patent Application 2011316807;

55. September 7, 2017 Notice of Grant for Patent issued by IP Australia in connection with Australian Patent Application

2011316807;

Non-Patent Literature

56. Casbon et al., "A method for counting PCT template molecules with application to next-generation sequencing", Nucleic Acids Res. vol. 39 no. 12 (July 2011);

57. Castle et al., "DNA copy number, including telomeres and mitochondria, assayed using next-generation sequencing," BMC Genomics vol. 11 no. 244 (2010);

58. Cheung V.G. & Nelson S.F., "Whole genome amplification using a degenerate oligonucleotide primer allows hundreds of genotypes to be performed on less than one nanogram of genomic DNA," PNAS vol. 93 no. 25 (Dec. 1996), p. 14676-79;

59. Chiang et al., "High-Resolution Mapping of Copy Number Alterations with Massively Parallel Sequencing," Nature Methods, vol. 6 no. 1 (2008), p. 99-103;

60. Craig et al., "Identification of Genetic Variants Using Bar-coded Multiplexed Sequencing," Nature Methods, vol. 5 no. 10 (Oct. 2008), p. 887-93;

61. Eid et al., "Real-Time DNA Sequencing from Single Polymerase Molecules," Science vol. 323 no. 5910 (Jan. 2009), p. 133-38;

62. Supporting Online Material for Eid et al., "Real-Time DNA Sequencing from Single Polymerase Molecules," accessible at www.sciencemag.org/cgi/content/full/1162986/DC1, (published Nov. 20, 2008);

63. Fu G.K. et al., "Counting individual DNA molecules by the stochastic attachment of diverse labels," PNAS vol. 108 no. 22 (May 2011), p. 9026-31;

64. Hiatt et al., "Parallel, tag-directed assembly of locally derived

short sequence reads," Nature Methods, vol. 7 no. 2 (2010), p.119-122;

65. Hug & Schuler, "Measurement of the Number of Molecules of a Single mRNA Species in a Complex mRNA Preparation," J. Theor. Biol., vol. 221 (2003), p. 615-624;

66. Islam et al., "Characterization of the single-cell transcriptional landscape by highly multiplex RNA-seq," Genome Res. vol. 21 no. 7 (July 2011) p. 1160-67;

67. Kivioja et al., "Counting absolute numbers of molecules using unique molecular identifiers, Nature Methods vol. 9 (2012), p. 72-74;

68. McCloskey M.L. et al, "Encoding PCR Products with Batch-stamps and Barcodes," Biochem. Genet. vol. 45 (Dec. 2007), p. 761-67;

69. Miner et al., "Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR," Nucleic Acids Res. vol. 32 no. 17 (2004), p. 1-4;

70. Meyerson et al., "Advances in Understanding Cancer Genomes Through Second-Generation Sequencing," Nature Reviews, vol. 11 (2010), p. 685-696;

71. Parameswaran et al., "A pyrosequencing-tailored nucleotide barcode design unveils opportunities for large-scale sample multiplexing," Nucleic Acids Res. vol. 35 no. 19 (2007);

72. Paunio T. et al., "Preimplantation diagnosis by whole genome amplification, PCT amplification, and solid-phase minisequencing of blastomere DNA," Clinical Chem. vol. 42 no. 9 (1996), p. 1382-90;

73. Plessy et al., "Linking promoters to functional transcripts in small samples with nanocage and CAGEscan," Nature Methods, vol. 7 no. 7 (2010), p. 528-534;

74. Shiroguchi at al., "Digital RNA sequencing minimizes sequence-dependent bias and amplification noise with optimized single-molecule barcodes," PNAS vol. 109 no. 4 (2012), p. 1347-52; and

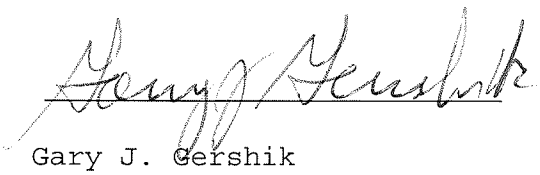
75. Technology Backgrounder: Single Molecule Real Time (SMRTTM) DNA Sequencing, Pacific Bioscience (2009).

The Examiner is respectfully requested to make of record each item listed on the substitute Form PTO-1449 by initialing and dating the attached substitute Form PTO-1449, and returning a copy of the initialed and dated form to applicants' undersigned attorney.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this First Information Disclosure Statement. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



Gary J. Gershik
Registration No. 39,992
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30 Rockefeller Plaza
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2019-04-19
Aditya Ramanathan Date

REMARKS

Claim 1 was pending in connection with the subject application with claims 2-67 previously cancelled. In this Amendment, applicants have cancelled claim 1 and added new claims 68-87.

Applicants respectfully request that this Amendment be entered. Accordingly, upon entry of this Amendment, claims 68-87 are pending and under consideration in the subject application.

Support for the claims may be found, *inter alia*, in the specification as filed as shown in the table below:

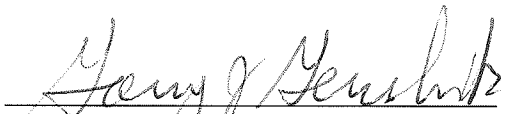
Claim	Specification
68	Page 58, lines 22-24; page 16, lines 2-25; Page 54, lines 17-19
69	Page 16, lines 2-4, page 18, lines 20-23; page 19, lines 22-24; page 8-9; page 51, line 10 to page 52, line 19; page 53, lines 9-21; Figure 8
70	Page 66, lines 19-24
71	Page 58, lines 18-20
72	Page 25, lines 20-21; page 51, lines 18-19
73	Page 24, lines 24-26
74	Page 32, line 15; page 39, lines 6-15
75	Page 56, lines 16-17
76	Page 17, lines 1-5
77	Page 17, lines 6-9
78	Page 17, lines 10-25
79	Page 17, line 26 to page 18, line 11
80	Page 18, lines 12-13
81	Page 22, line 16 to page 23, line 12
82	Page 23, line 13 to page 24, line 8
83	Page 24, lines 9-10
84	Page 25, lines 17-19
85	Page 25, lines 24-27

86	Page 26, lines 4-22
87	Page 26, lines 4-22

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Second Preliminary Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

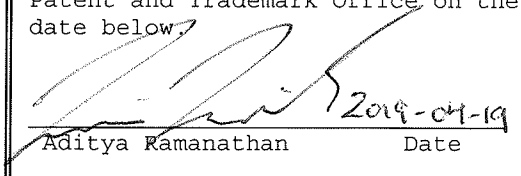
Respectfully submitted,



Gary J. Gershik
Registration No. 39,992
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2019-04-19

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IPR2025-01353
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Electronic Acknowledgement Receipt

EFS ID:	35778365
Application Number:	16269818
International Application Number:	
Confirmation Number:	8088
Title of Invention:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
First Named Inventor/Applicant Name:	James Hicks
Customer Number:	23432
Filer:	Gary J. Gershik/Darren Haber
Filer Authorized By:	Gary J. Gershik
Attorney Docket Number:	81503-AAA/GJG/ADR
Receipt Date:	19-APR-2019
Filing Date:	07-FEB-2019
Time Stamp:	14:22:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		190419_81503-AAA_Second_Preliminary_Amendment_ADR.pdf	349232 fb3dd3d0c02beefe91632f4eb0d67b8e6b2989e3	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	7
	Applicant Arguments/Remarks Made in an Amendment	8	9

Warnings:					
Information:					
2		190419_81503-AAA_First_IDS_ADR.pdf	740851 66c3fa834ca2b78aacb8c95c56a505f0734a72b5	yes	14

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	10
	Information Disclosure Statement (IDS) Form (SB08)	11	14

Warnings:	
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Total Files Size (in bytes):	1090083

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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.

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 5981/81503-AAA/GJG/ADR	Application No. 16/269,818
Information Disclosure Statement by Applicant (Use several sheets if necessary)		First Named Inventor James Hicks	Confirmation Number 8088
(37 CFR §1.98(b))		Filing Date February 7, 2019	Group Art Unit Not yet assigned

U.S. Patent Documents

Examiner Initial	Cite ID[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM/DD/YYYY	First named inventor
	1	9,670,536	6/6/2018	Casbon
	2	9,487,829	11/8/2016	Vogelstein
	3	9,476,095	10/25/2016	Vogelstein
	4	9,404,156	8/2/2016	Hicks
	5	8,741,606	6/3/2014	Casbon
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	7	8,663,917	3/4/2014	Wigler
	8	8,554,488	10/8/2013	Wigler
	9	8,273,871	9/25/2012	Hannon
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	23	2012/0328607	12/27/2012	Hicks
	24	2012/0149593	6/14/2012	Hicks
	25	2010/0227768	9/10/2010	Wigler
	26	2010/0203538	8/12/2010	Dube

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	27	2010/178655	7/15/2010	Hamilton
	28	2009/0137402	5/28/2009	Wang
	29	2008/0261204	10/23/2008	Lexow
	30	2007/0207481	9/6/2007	Wigler
	31	2007/0172873	7/26/2007	Brenner
	32	2007/0020640	1/25/2007	McCloskey
	33	2006/0073506	4/6/2006	Christians
	34	2006/0035258	2/16/2006	Tadakamalla
	35	2005/0266444	12/1/2005	Wigler
	36	2005/0032095	2/10/2005	Wigler
	37	2004/110153	6/10/2004	Dong

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Cite ID[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM/DD/YYYY	Country or Patent Office[3]	Class	T[6]
	38	WO 2012/054873	4/26/2012	WO		
	39	WO 2007/062445	6/7/2007	WO		
	40	DE 10 2008 025 656 A1	12/3/2009	DE		

NON PATENT LITERATURE DOCUMENTS

Examiner Initial	Cite ID[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.
	41	June 26, 2012 International Search Report issued in connection with PCT International Application No. PCT/US2011/057350 (WO 2012/054873)
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	58	Cheung V.G. & Nelson S.F., "Whole genome amplification using a degenerate oligonucleotide primer allows hundreds of genotypes to be performed on less than one nanogram of genomic DNA," PNAS vol. 93 no. 25 (Dec. 1996), p. 14676–79
	59	Chiang et al., "High-Resolution Mapping of Copy Number Alterations with Massively Parallel Sequencing," Nature Methods, vol. 6 no. 1 (2008), p. 99-103
	60	Craig et al., "Identification of Genetic Variants Using Bar-coded Multiplexed Sequencing," Nature Methods, vol. 5 no. 10 (Oct. 2008), p. 887-93
	61	Eid et al., "Real-Time DNA Sequencing from Single Polymerase Molecules," Science vol. 323 no. 5910 (Jan. 2009), p. 133-38

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	62	Supporting Online Material for Eid et al., "Real-Time DNA Sequencing from Single Polymerase Molecules," accessible at www.sciencemag.org/cgi/content/full/1162986/DC1, (published Nov. 20, 2008)
	63	Fu G.K. et al., "Counting individual DNA molecules by the stochastic attachment of diverse labels," PNAS vol. 108 no. 22 (May 2011), p. 9026-31
	64	Hiatt et al., "Parallel, tag-directed assembly of locally derived short sequence reads," Nature Methods, vol. 7 no. 2 (2010), p.119-122
	65	Hug & Schuler, "Measurement of the Number of Molecules of a Single mRNA Species in a Complex mRNA Preparation," J. Theor. Biol., vol. 221 (2003), p. 615-624
	66	Islam et al., "Characterization of the single-cell transcriptional landscape by highly multiplex RNA-seq," Genome Res. vol. 21 no. 7 (July 2011) p. 1160-67
	67	Kivioja et al., "Counting absolute numbers of molecules using unique molecular identifiers, Nature Methods vol. 9 (2012), p. 72-74
	68	McCloskey M.L. et al, "Encoding PCR Products with Batch-stamps and Barcodes," Biochem. Genet. vol. 45 (Dec. 2007), p. 761-67
	69	Miner et al., "Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR," Nucleic Acids Res. vol. 32 no. 17 (2004), p. 1-4
	70	Meyerson et al., "Advances in Understanding Cancer Genomes Through Second-Generation Sequencing," Nature Reviews, vol. 11 (2010), p. 685-696
	71	Parameswaran et al., "A pyrosequencing-tailored nucleotide barcode design unveils opportunities for large-scale sample multiplexing," Nucleic Acids Res. vol. 35 no. 19 (2007)
	72	Paunio T. et al., "Preimplantation diagnosis by whole genome amplification, PCT amplification, and solid-phase minisequencing of blastomere DNA," Clinical Chem. vol. 42 no. 9 (1996), p. 1382-90
	73	Plessy et al., "Linking promoters to functional transcripts in small samples with nanocage and CAGEscan," Nature Methods, vol. 7 no. 7 (2010), p. 528-534
	74	Shiroguchi at al., "Digital RNA sequencing minimizes sequence-dependent bias and amplification noise with optimized single-molecule barcodes," PNAS vol. 109 no. 4 (2012), p. 1347-52
	75	Technology Backgrounder: Single Molecule Real Time (SMRTTM) DNA Sequencing, Pacific Bioscience (2009)

Examiner Signature	Date Considered

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Substitute Disclosure Form (PTO-1449)

IPR2025-01353
FIRST IDS EXHIBIT A
CSHL EX2001

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Cancelled).

2.-67. (Cancelled).

68. (New) A method for measuring the mutational load of a genomic sample, comprising:

a. obtaining segments of nucleic acids from the genome sample;

b. tagging the segments with nucleic acid tags, thereby generating unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a portion corresponding to a segment of the segments of the nucleic acids from step (a) and a portion corresponding to a nucleic acid tag of the nucleic acid tags;

c. subjecting the tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified tagged nucleic acid molecules;

d. generating tag associated sequence reads by sequencing the amplified tagged nucleic acid molecules of step (c);

e. assigning each of the amplified tagged nucleic acid molecules to a location on a genome by mapping the subsequence associated with the nucleic acids of each of the tag associated sequence read of step (d); and

f. accounting for sequence error during processing comprising identifying tagged nucleic acid molecules that have mutated during the amplification of step c) and ignoring so mutated tagged nucleic acid molecules,

thereby measuring the mutational load of the genomic sample.

69. (New) The method of claim 68, wherein the segments of nucleic acids are selected from any one of the following: genomic nucleic acids, RNA, mRNA transcripts, or cDNA from mRNA transcripts.

70. (New) The method of claim 69, further comprising obtaining a genomic profile from the genomic sample, obtaining an expression profile from the genomic sample, or obtaining copy number information from the genomic sample.

71. (New) The method of claim 68, wherein the polymerase chain reaction of step c) comprises region specific PCR primers.

72. (New) The method of claim 68, wherein the unique tagged nucleic acid molecules differ at more than one nucleotide or wherein the sequence of individual nucleic acid tags is known prior to generating tagged nucleic acid molecules.

73. (New) The method of claim 69, wherein the segments of the nucleic acids are segments of genomic nucleic acids, and are produced by mechanical shearing, heating, or sonication of the genome sample.

74. (New) The method of claim 68, wherein the nucleic acid tags comprise a sample tag or a sample tag set.

75. (New) The method of claim 68, wherein the tag is double-stranded.

76. (New) The method of claim 68, further comprising estimating the mutational load of a single region of the genome comprising more than one location by assigning as the mutational load the location with the highest mutational load obtained in step (f) for the locations within the region.

77. (New) The method of claim 68, further comprising comparing the mutational load of a location in step (f) to the same location on

the reference sample, thereby estimating a relative mutational load of the location.

78. (New) The method of claim 68, further comprising

g. determining the mutational load of locations of the genome in step (f) which comprise a first region of the genome, wherein the first region comprises more than one location;

h. determining the mutational load of locations of the genome in step (f) for locations on the genome which comprise a second region of the genome, wherein the second region is comprised of a number of locations which is comparable to the number of locations of the first region,

i. comparing the mutational load obtained in step (g) to the mutational load obtained in step (h),

thereby estimating the relative mutational load of the first region of the genome to the mutational load of the second region of the genome.

79. (New) The method of claim 78, wherein step (h) further comprises

j. determining the mutation load of the genome in step (f) for locations on the genome which comprise a third region of the genome, wherein the third region is comprised of a number of locations which is comparable to the number of locations of the first region;

k. obtaining an average of the mutational load determined in step (f) for locations which comprise the second region and the mutational load obtained in step (f) for locations which comprise the third region.

80. (New) The method of claim 78, wherein the second region comprises

a centromere.

81. (New) The method of claim 68, wherein said tagging the segments comprises:

i) adding a polynucleotide tail to the ends of the segments of the genomic nucleic acids to generate zero-th order derivative strands comprising the polynucleotide tail;

ii) subjecting the zero-th order derivative strands of step (i) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement of the zero-th order derivative strands, thereby generating first order derivative strands;

iii) adding a polynucleotide tail to the first order derivative strands, thereby generating a first order derivative strands comprising the polynucleotide tail;

iv) subjecting the first order derivative strands comprising the polynucleotide tail to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the first order derivative strands under conditions that promote the formation of only one complement of the first order derivative strands comprising the polynucleotide tail, thereby generating second order derivative strands,

wherein the primers of at least one of steps ii) and iv) comprise

nucleic acid tags, such that each tagged nucleic acid molecule is unique, and the first order derivative strands and the second order derivative strands are the tagged nucleic acid molecules.

82. (New) The method of claim 68, wherein said tagging the segments comprises:

i) adding a polynucleotide tail to the ends of the segments of genomic nucleic acids, thereby generating zero-th order derivative strands comprising the polynucleotide tail,

ii) subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

iii) subjecting the product of step (ii) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (i) under conditions which promote the formation of only one complement of the product of step (ii), wherein the primers of step (ii) and the primers of step (iii) have different nucleotide sequences, and wherein the polymerase has 3′-5′ proofreading activity,

wherein the primers of at least one of steps (ii) and (iii) comprise nucleic acid tags, such that each tagged nucleic acid molecule is unique, thereby generating each unique tagged nucleic acid molecule.

83. (New) The method of claim 81, wherein said adding the polynucleotide tail comprises the use of a terminal transferase.

84. (New) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to PCR or the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d).

85. (New) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCT or prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c).

86. (New) The method of claim 85, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads.

87. (New) The method of claim 68, wherein the tag associated sequence reads are generated from a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	James Hicks et al.	
U.S. Serial No.	:	16/269,818	Examiner: Lu, Frank W.M.
Filing Date	:	February 7, 2019	Art Unit: 1634
Confirmation No.	:	8088	
For	:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION	

30 Rockefeller Plaza
20th Floor
New York, New York 10112
April 19, 2019

BY EFS
Commissioner for Patents
Alexandria, VA

SECOND PRELIMINARY AMENDMENT

This Preliminary Amendment is being submitted in connection with the above-identified continuation application prior to the mailing of the first Office Action.

Please amend the subject application as follows:

Amendments to the Claims begin on page **2** of this paper.

Remarks begin on page **8** of this paper.

IPR2025-01353
CSHL EX2001

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR

CONFIRMATION NO. 8088

PUBLICATION NOTICE

23432
COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

OC000000108416193

Title:VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Publication No.US-2019-0153535-A1
Publication Date:05/23/2019

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/AIA/96 (08-12)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Cold Spring Harbor Laboratory

Application No./Patent No.: 16/269,818 Filed/Issue Date: February 7, 2019

Titled: Varietal Counting of Nucleic Acids for Obtaining Genomic Copy Number Information

Cold Spring Harbor Laboratory, 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 027537, Frame 0950/0955, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

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.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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4. From: _____ To: _____

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5. From: _____ To: _____

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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.

Gary J. Gershik — Signature

March 11, 2020 — Date

Gary J. Gershik — Printed or Typed Name

39,992 — 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.
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 Acknowledgement Receipt

EFS ID:	38830949
Application Number:	16269818
International Application Number:	
Confirmation Number:	8088
Title of Invention:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
First Named Inventor/Applicant Name:	James Hicks
Customer Number:	23432
Filer:	Gary J. Gershik/Darren Haber
Filer Authorized By:	Gary J. Gershik
Attorney Docket Number:	81503-AAA/GJG/ADR
Receipt Date:	11-MAR-2020
Filing Date:	07-FEB-2019
Time Stamp:	11:40:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73	200316_81503_AAA_373Statement_JTS.pdf	193166 455063451ccb3351f12c80197ad137249a7da6d0	no	3

Warnings:

IPR2025-01353
CSHL EX2001

Information:	
Total Files Size (in bytes):	193166

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.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 08/25/2020

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
08/25/2020	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):

DUSPTO@cooperdunham.com
patcomm-in-grp@cooperdunham.com
pdocketing@cooperdunham.com

Office Action Summary	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	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 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/19/2019.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 68-87 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 68-87 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

Preliminary Amendment

1. The preliminary amendment filed on April 19, 2019 has been entered. The claims pending in this application are claims 68-87.

Election/Restrictions

2. This application contains claims directed to the following patentably distinct species:

(1) the segments of nucleic acids are genomic nucleic acids (claims 69, 70, and 73)

(2) the segments of nucleic acids are RNA or mRNA transcripts (claim 69)

(3) the segments of nucleic acids are cDNA from mRNA transcripts (claim 69)

The species are independent or distinct because these species are directed to different nucleic acids which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71, 72, and 74-87.

There is a search and/or examination burden for the patentably distinct species as set forth above because the searches for species (1) to (3) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An

argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

3. This application further contains claims directed to the following patentably distinct species:

(4) further obtaining a genomic profile from the genomic sample (claim 70)

(5) further obtaining an expression profile from the genomic sample (claim 70)

(6) further obtaining copy number information from the genomic sample (claim 70)

The species are independent or distinct because these species are directed to different information which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 69, and 71-87.

There is a search and/or examination burden for the patentably distinct species as set forth above because the searches for species (4) to (6) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. This application further contains claims directed to the following patentably distinct species:

(7) the unique tagged nucleic acid molecules differ at more than one nucleotide (claim 72)

(8) the sequence of individual nucleic acid tags is known prior to generating tagged nucleic acid molecules (claim 72)

The species are independent or distinct because these species are directed to different method step options for the method of clam 68. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68-71 and 73-87.

There is a search and/or examination burden for the patentably distinct species as set forth above because the searches for species (7) and (8) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

5. This application further contains claims directed to the following patentably distinct species:

(9) the nucleic acid tags comprise a sample tag (claim 74, 85, and 86)

(10) the nucleic acid tags comprise a sample tag set (claim 74, 85, and 86)

The species are independent or distinct because these species are directed to different options for the nucleic acid tags. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68-73, 75-84, and 87.

There is a search and/or examination burden for the patentably distinct species as set forth above because the searches for species (9) and (10) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered

timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

6. This application further contains claims directed to the following patentably distinct species:

(11) subjecting the zero-th order derivative strands of step (i) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement of the zero-th order derivative strands (claim 81)

(12) subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5' ends of the zero-th order derivative strands (claim 82)

The species are independent or distinct because these species are directed to different methods for tagging the segments. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68-80 and 83-87.

There is a search and/or examination burden for the patentably distinct species as set forth above because the searches for species (11) and (12) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

7. This application further contains claims directed to the following patentably distinct species:

(13) the unique tagged nucleic acid molecules are subjected to hybrid capture prior to PCR (claim 84)

(14) the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d) (claim 84)

The species are independent or distinct because these species are directed to different method step options for the method of claim 68. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68-83 and 85-87.

There is a search and/or examination burden for the patentably distinct species as set forth above because the searches for species (13) and (14) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

8. This application further contains claims directed to the following patentably distinct species:

(15) the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR (claims 85 and 86)

(16) the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c) (claims 85 and 86)

The species are independent or distinct because these species are directed to different method step options for the method of claim 68. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68-84 and 87.

There is a search and/or examination burden for the patentably distinct species as set forth above because the searches for species (15) and (16) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

9. This application further contains claims directed to the following patentably distinct species:

(17) the tag associated sequence reads are generated from a single species or a single cell (claim 87)

(18) the tag associated sequence reads are generated from two or more organisms, two or more species, or from a population of microbes (claim 87)

The species are independent or distinct because these species are directed to different tag associated sequence reads which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68-86.

There is a search and/or examination burden for the patentably distinct species as set forth above because the searches for species (17) and (18) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571)272-0731.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
August 18, 2020

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 8088

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/269,818	02/07/2019 RULE	435	1634	81503-AAA/GJG/ADR

APPLICANTS

Cold Spring Harbor Laboratory, Cold Spring Harbor, NY;

INVENTORS

James Hicks, Locust Valley, NY;
Nicholas Navin, Houston, TX;
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Zihua Wang, Huntington, NY;
Michael Wigler, Cold Spring Harbor, NY;

**** CONTINUING DATA ***************************

This application is a CON of 15/063,278 03/07/2016
which is a CON of 13/278,333 10/21/2011 PAT 9404156
which claims benefit of 61/510,579 07/22/2011
and claims benefit of 61/406,067 10/22/2010

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
02/14/2019

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
❑ Yes ☑ No	❑ Yes ❑ No	/FRANK LU/ Examiner's Signature	❑ Initials	NY	15	1	1

ADDRESS

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112
UNITED STATES

TITLE

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

FILING FEE RECEIVED		
785	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

Electronic Patent Application Fee Transmittal

Application Number:	16269818
Filing Date:	07-Feb-2019
Title of Invention:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
First Named Inventor/Applicant Name:	James Hicks
Filer:	Gary J. Gershik/Darren Haber
Attorney Docket Number:	81503-AAA/GJG/ADR

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	740	740
Miscellaneous:				
			Total in USD ($)	**740**

REMARKS

Elections/Restrictions

I. Species Election 1

On page 2 of the August 25, 2020 Office Action, the Examiner alleged that the subject application contains claims directed to the following patentably distinct species:

(1) the segments of nucleic acids are genomic nucleic acids (claims 69, 70, and 73)

(2) the segments of nucleic acids are RNA or mRNA transcripts (claim 69)

(3) the segments of nucleic acids are cDNA from mRNA transcripts (claim 69)

Applicant's response

In response, applicant elects:

(1) the segments of nucleic acids are genomic nucleic acids (claims 69, 70, and 73)

Claims 68-87 read on the elected species.

II. Species Election 2

On page 3 of the August 25, 2020 Office Action, the Examiner alleged that the subject application contains claims directed to the following patentably distinct species:

(4) further obtaining a genomic profile from the genomic sample (claim 70)

(5) further obtaining an expression profile from the genomic sample (claim 70)

(6) further obtaining copy number information from the genomic sample (claim 70)

Applicant's response

In response, applicant elects:

(4) further obtaining a genomic profile from the genomic sample (claim 70)

Claims 68-87 read on the elected species.

III. Species Election 3

On page 5 of the August 25, 2020 Office Action, the Examiner alleged that the subject application contains claims directed to the following patentably distinct species:

(7) the unique tagged nucleic acid molecules differ at more than one nucleotide (claim 72)

(8) the sequence of individual nucleic acid tags is known prior to generating tagged nucleic acid molecules (claim 72)

Applicant's response

In response, applicant elects:

(8) the sequence of individual nucleic acid tags is known prior to generating tagged nucleic acid molecules (claim 72)

Claims 68-87 read on the elected species.

IV. Species Election 4

On page 7 of the August 25, 2020 Office Action, the Examiner alleged that the subject application contains claims directed to the following patentably distinct species:

(9) the nucleic acid tags comprise a sample tag (claim 74, 85, and 86)

(10) the nucleic acid tags comprise a sample tag set (claim 74, 85, and 86)

Applicant's response

In response, applicant elects:

(9) the nucleic acid tags comprise a sample tag (claim 74, 85, and 86)

Claims 68-87 read on the elected species.

V. Species Election 5

On page 8 of the August 25, 2020 Office Action, the Examiner alleged that the subject application contains claims directed to the following patentably distinct species:

(11) subjecting the zero-th order derivative strands of step (i) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement of the zero-th order derivative strands (claim 81)

(12) subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5' ends of the zero-th order derivative strands (claim 82)

Applicant's response

In response, applicant elects:

(12) subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5' ends of the zero-th order derivative strands (claim 82)

Claims 68-80 and 82-87 read on the elected species.

VI. Species Election 6

On page 10 of the August 25, 2020 Office Action, the Examiner alleged that the subject application contains claims directed to the following patentably distinct species:

(13) the unique tagged nucleic acid molecules are subjected to hybrid capture prior to PCR (claim 84)

(14) the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d) (claim 84)

Applicant's response

In response, applicant elects:

(14) the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d) (claim 84)

Claims 68-87 read on the elected species.

VII. Species Election 7

On page 12 of the August 25, 2020 Office Action, the Examiner alleged that the subject application contains claims directed to the following patentably distinct species:

(15) the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR (claims 85 and 86)

(16) the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c) (claims 85 and 86)

Applicant's response

In response, applicant elects:

(16) the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c) (claims 85 and 86)

Claims 68-87 read on the elected species.

VIII. Species Election 8

On page 13 of the August 25, 2020 Office Action, the Examiner alleged that the subject application contains claims directed to the following patentably distinct species:

(17) the tag associated sequence reads are generated from a single species or a single cell (claim 87)

(18) the tag associated sequence reads are generated from two or more organisms, two or more species, or from a population of microbes (claim 87)

Applicant's response

In response, applicant elects:

(17) the tag associated sequence reads are generated from a single species or a single cell (claim 87)

Claims 68-87 read on the elected species.

IX. Entitlement to Examination of Other Species

Applicants note that where, as here, applicant elects a species, and that species is found allowable, then applicant will be entitled to examination of other species. The examination of other species shall be guided by the logic of the dependent claims readable on the elected species, such that the species falling into the narrowest claim that reads on the allowable species will be examined next, and so on.

Once a generic claim is found allowable, applicant will be entitled to consideration of claims to additional species which are written in

dependent form or otherwise require all the limitations of the allowed generic claim.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the fee of seven hundred forty dollars ($740.00) for a small entity for a three-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

/Gary J. Gershik/

Gary J. Gershik
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Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on January 25, 2021.

/Darren Haber/

Darren Haber

Electronic Acknowledgement Receipt

EFS ID:	41733512
Application Number:	16269818
International Application Number:	
Confirmation Number:	8088
Title of Invention:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
First Named Inventor/Applicant Name:	James Hicks
Customer Number:	23432
Filer:	Gary J. Gershik/Darren Haber
Filer Authorized By:	Gary J. Gershik
Attorney Docket Number:	81503-AAA/GJG/ADR
Receipt Date:	25-JAN-2021
Filing Date:	07-FEB-2019
Time Stamp:	14:38:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$740
RAM confirmation Number	E20211OE38470274
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

IPR2025-01353
CSHL EX2001

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	210125_81503-AAA_Response_DH.pdf	98554 f15230f133b5201824b01c72c89749c6127534b2	no	7
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31054 a94dd26ef4d50428d4e3538e42cdb42c9e27856d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	129608		

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(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

90 Park Avenue
21st Floor
New York, NY 10016
January 25, 2021

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

COMMUNICATION IN RESPONSE TO AUGUST 25, 2020 OFFICE ACTION AND PETITION FOR THREE-MONTH EXTENSION OF TIME

This Communication is submitted in response to the August 25, 2020 Office Action issued in connection with the above-identified application. A response to the August 25, 2020 Office Action was originally due October 25, 2020. Applicants hereby petition for a three-month extension of time. The fee for a three-month extension of time is seven hundred forty dollars ($740.00) for a small entity and authorization is hereby given to charge this amount to Deposit Account No. 03-3125. With a three-month extension of time, a response is now due January 25, 2021. Accordingly, this Communication is being timely filed.

Remarks begin on page **2** of this paper.

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(FILE 'HOME' ENTERED AT 23:41:20 ON 26 MAR 2021)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH, EMBASE' ENTERED AT 23:44:52 ON
     26 MAR 2021
L1          5561 S MUTATIONAL LOAD
L2          1225 S SEQUENCE ERROR OR SEQUENCE MISTAKE
L3        888832 S TAG OR ADAPTOR OR ADAPTER OR LINKER
L4       5388757 S PCR OR AMPLIFYING OR AMPLIFY OR AMPLIFICATION OR EXTENSION OR
L5       1574469 S MAPPING
L6             0 S L1 AND L2 AND L3 AND L4 AND L5
L7             0 S L1 AND L2 AND L3 AND L4
L8             0 S L1 AND L2 AND L3
L9             0 S L1 AND L2 AND L3 AND L5
L10            0 S L1 AND L2
L11           32 S L1 AND L3
L12           23 DUP REM L11 (9 DUPLICATES REMOVED)
L13          737 S L1 AND L4
L14           22 S L1 AND L4 AND L5
L15           14 DUP REM L14 (8 DUPLICATES REMOVED)
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	Mutational near load same sequence near5 (error or mistake) same (tag or adaptor or adapter or linker) same (PCR or amplifying or amplify or amplification or extension or extense or extensing) same mapping	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:28
L2	0	Mutational near load same sequence near5 (error or mistake) same (tag or adaptor or adapter or linker)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:29
L3	0	mutational near load same sequence near5 (error or mistake) same (tag or adaptor or adapter or linker)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:29
L4	1	mutational near load same sequence near5 (error or mistake)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:30
L5	646	mutational near load	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:30
L6	0	mutational near load same (tag or adaptor or adapter or linker) same (PCR or amplifying or amplify or amplification or extension or extense or extensing) same mapping	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:31
L7	1	mutational near load same(PCR or amplifying or amplify or amplification or extension or extense or extensing) same mapping	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:31

L8	100	mutational near load same(PCR or amplifying or amplify or amplification or extension or extense or extensing)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:31
L9	7	mutational near load same mapping	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:32
L10	7	9 AND ((C12Q1/6886 OR C12Q1/6827 OR C12Q2600/156 OR C12Q1/6806 OR C12Q1/6858 OR C12Q1/686 OR C12Q1/6869 OR C12Q2531/113 OR C12Q2565/30 OR C12Q2565/514 OR C12Q2565/625 OR C12Q2600/112 OR C12Q2600/158 OR C12Q2600/16 OR C12Q2535/122 OR C12Q2600/154 OR A61P35/00 OR A61P15/00 OR A61P19/02 OR A61P1/00 OR A61P25/00 OR A61P27/02 OR A61P29/00 OR A61P31/04 OR A61P3/10 OR A61P9/00 OR G01N2800/56 OR G01N2800/60 OR G16B20/00 OR G16B30/00 OR A61K38/00 OR A61K48/005 OR C07K16/08 OR C07K16/1275 OR C07K16/2803 OR C07K2317/21 OR C12N15/111 OR C12N15/86 OR C12N2310/20 OR C12N2750/14143 OR C12N9/22).CPC.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/03/26 23:41

3/26/2021 11:42:29 PM
C:\Users\flu\Documents\EAST\Workspaces\~auto.01112018.114853.bak.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	Art Unit
	FRANK W LU	1634

CPC - Searched*		
Symbol	Date	Examiner
see attached file	03/26/2021	/FL/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
see attached file	03/26/2021	/FL/

US Classification - Searched*			
Class	Subclass	Date	Examiner
435	6.1, 6.11, 6.12, 91.1, 91.2, 91.51	03/26/2021	/FL/
436	94, 501	03/26/2021	/FL/
536	23.1, 24.3, 24.33, 25.3	03/26/2021	/FL/

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STN and EAST (see attached files) and Inventor Searches	03/26/2021	/FL/

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

/FRANK W LU/ Primary Examiner, Art Unit 1634	March 26, 2021

IPR2025-01353
GSNL 2002001

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 04/01/2021
COOPER & DUNHAM LLP
90 PARK AVENUE, 21 ST. FLOOR
NEW YORK, NY 10016

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
04/01/2021	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):

DUSPTO@cooperdunham.com
patcomm-in-grp@cooperdunham.com
pdocketing@cooperdunham.com

Office Action Summary	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	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 1/25/2021.

☐ 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) 68-87 is/are pending in the application.

5a) Of the above claim(s) 81 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68-80 and 82-87 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 2/7/2019 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 4/19/2019.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of species (1) (the segments of nucleic acids are genomic nucleic acids (claims 69, 70, and 73), species (4) (further obtaining a genomic profile from the genomic sample, see claim 70), species (8) (the sequence of individual nucleic acid tags is known prior to generating tagged nucleic acid molecules, see claim 72), species (9) (the nucleic acid tags comprise a sample tag, see claim 74, 85, and 86), species (12) (subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5' ends of the zero-th order derivative strands, see claim 82), species (14) (the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d), see claim 84), species (16) (the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c), see claims 85 and 86), and species (17) (the tag associated sequence reads are generated from a single species or a single cell, see claim 87) in the reply filed on January 15, 2021 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.01(a)). Claims 68-80 and 82-87 will be examined.

Specification

2. The disclosure is objected to because of the following informality: since case 15/063,278 has been patented, applicant is required to update this information in the first paragraph of the specification.

Appropriate correction is required.

Claim Objections

3. Claim 68 is objected to because of the following informalities: (1) no period should appear after the label of each step, e.g., "a." should be --a)--; (2) "during processing" in step f) should be deleted; and (3) "the amplification of step (c)" should be "the PCR of step (c)".

4. Claim 72 is objected to because of the following informality: "the sequence of individual nucleic acid tags is known prior to generating tagged nucleic acid molecules" should be "the sequences of the nucleic acid tags are known prior to said generating tagged nucleic acid molecules".

5. Claim 75 is objected to because of the following informality: "the tag is" should be "the nucleic acid tags are".

6. Claim 78 is objected to because of the following informality: no period should appear after the label of each step, e.g., "g." should be --g)--.

7. Claim 79 is objected to because of the following informality: no period should appear after the label of each step, e.g., "j." should be --j)--.

8. Claim 78 is objected to because of the following informalities: (1) "determining the mutational load of locations of the genome in step (f) which comprise a first region of the genome" should be "determining the mutational load of a first region of the genome in step (f)";

(2) "determining the mutational load of locations of the genome in step (f) which comprise a second region of the genome" should be "determining the mutational load of a second region of the genome in step (f)"; and (3) "is comprised of" should be "comprises".

9. Claim 79 is objected to because of the following informalities: (1) "determining the mutational load of the genome in step (f) for the locations on the genome which comprise a third region of the genome" should be "determining the mutational load of a third region of the genome in step (f)"; (2) "is comprised of" should be "comprises"; and (3) "obtaining an average of the mutational load determined in step (f) for locations which comprise the second region and the mutational load obtained in step (f) for locations which comprise the third region" should be "obtaining an average of the mutational load of the mutational load of the second region and the mutational load of the third region".

10. Claim 82 is objected to because of the following informality: "such that each tagged nucleic acid molecule is unique, thereby generating each unique tagged nucleic acid molecule" should be "such that each of the tagged nucleic acid molecule is unique, thereby generating the unique tagged nucleic acid molecules".

11. Claim 85 is objected to because of the following informality: "the PCT" should be "the PCR".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. 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.

13. New Matter

Claims 68-80 and 82-87 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.

Newly added independent claim 68 contains a limitation "accounting for sequence error during processing comprising identifying tagged nucleic acid molecules that have mutated during the amplification of step c) and ignoring so mutated tagged nucleic acid molecules", newly added claim 76 contains a limitation "estimating the mutational load of a single region of the genome comprising more than one location by assigning as the mutational load the location with the highest mutational load obtained in step (f) for the locations within the region", newly added claim 77 contains a limitation "comparing the mutational load of a location in step (f) to the same location on the reference sample, thereby estimating a relative mutational load of the location", newly added claim 78 contains a limitation "g) determining the mutational load of locations of the genome in step (f) which comprise a first region of the genome, wherein the first region comprises more than one location; h) determining the mutational load of locations of the genome in step (f) for locations on the genome which comprise a second region of the genome,

wherein the second region is comprised of a number of locations which is comparable to the number of locations of the first region; i) comparing the mutational load obtained in step (g) to the mutational load obtained in step (h), thereby estimating the relative mutational load of the first region of the genome to the mutational load of the second region of the genome", and newly added claim 79 contains a limitation "j) determining the mutation load of the genome in step (f) for locations on the genome which comprise a third region of the genome, wherein the third region is comprised of a number of locations which is comparable to the number of locations of the first region; k) obtaining an average of the mutational load determined in step (f) for locations which comprise the second region and the mutational load obtained in step (f) for locations which comprise the third region". Although the specification describes that "[T]hrough sequence error during processing, the tag may very occasionally mutate, creating the appearance of a new tagged nucleic acid molecule. But if the set of tags are sufficiently large, the tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting" and "[T]he above description is of methodology designed to measure copy number and mutational loads throughout much of the genome in single cells" (see paragraphs [0297] and [0307] of US 2019/0153535 A1, which is US application of this instant application), page 16, lines 2-25, page 17, lines 1-25, page 18, lines 1-11, page 54, lines 17-19, and page 58, lines 22-24 of the specification suggested by applicant do not describe such limitations recited in claims 68 and 76-79 since the specification does not describe 1) accounting for sequence error comprising identifying tagged nucleic acid molecules that have mutated during the amplification of step c) and ignoring so mutated tagged nucleic acid molecules; 2) measuring the mutational load of the genomic sample based on the method of claim 68; 3) estimating the mutational load of a single

region of the genome; 4) comparing the mutational load of a location in step (f) to the same location on the reference sample, and 5) determining the mutational load of locations of the genome in step (f).

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

14. Scope of Enablement

Claims 68-80 and 82-87 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, because the specification, while being enabling for performing steps a) to c) of claim 68, does not reasonably provide enablement for measuring the mutational load of a genomic sample using the methods recited in claims 68-80 and 82-87. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Nature of The Invention

The claims are drawn to a method for measuring the mutational load of a genomic sample. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.,* 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of The Claims

Claims 68-80 and 82-87 encompass a method for measuring the mutational load of a genomic sample, comprising: a) obtaining segments of nucleic acids from the genome sample; b) tagging the segments with nucleic acid tags, thereby generating unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a portion corresponding to a segment of the segments of the nucleic acids from step (a) and a portion corresponding to a nucleic acid tag of the nucleic acid tags; c) subjecting the tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified tagged nucleic acid molecules; d) generating tag associated sequence reads by sequencing the amplified tagged nucleic acid molecules of step (c); e) assigning each of the amplified tagged nucleic acid molecules to a location on a genome by mapping the subsequence associated with the nucleic acids of each of the tag associated sequence read of step (d); and f) accounting for sequence error during processing comprising identifying tagged nucleic acid molecules that have mutated during the amplification of step c) and ignoring so mutated tagged nucleic acid molecules.

Working Examples

The specification provides working examples: (1) Methylation Sequencing; (2) Comparative Genomic Hybridization (CGE) by High Throughput Sequencing; (3) Single Cell Microarray and Sequencing; (4) Sequencing Across Chromosome Breakpoints; and (5) Copy Number Profiling Using Varietal Tags on Restriction Enzyme Fragments (see pages 57-67).

The Amount of Direction or Guidance Provided and The State of The Prior Art

The specification provides working examples: (1) Methylation Sequencing; (2) Comparative Genomic Hybridization (CGE) by High Throughput Sequencing; (3) Single Cell Microarray and Sequencing; (4) Sequencing Across Chromosome Breakpoints; and (5) Copy Number Profiling Using Varietal Tags on Restriction Enzyme Fragments (see pages 57-67). However, the specification provides no working example for measuring the mutational load of a genomic sample using the methods recited in claims 68-80 and 82-87. During the process of the prior art search, the examiner has not found any prior art which is related to measure the mutational load of a genomic sample using the methods recited in claims 68-80 and 82-87.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether the mutational load of a genomic sample can be measured using the methods recited in claims 68-80 and 82-87.

It is known that "[M]utational load is the total genetic burden in a population resulting from accumulated deleterious mutations. It is a kind of genetic load. It can be thought of as a

balance between selection against a deleterious gene and its production by mutation. At the equilibrium, a dominant deleterious mutation has a frequency of m/s, where m is the mutation rate and s is the selective disadvantage of the mutation. In this case the mutational load can be calculated to be equal to the mutation rate. The load expresses the fact that individuals are dying because of the deleterious mutations that arise. The population carries a load of deleterious mutations, which reduce the average fitness of its members" (see "Mutational load"). Although the specification shows that "[T]he above description is of methodology designed to measure copy number and mutational loads throughout much of the genome in single cells" (see paragraph [0307] of US 2019/0153535 A1, which is US application of this instant application), since the specification does not have a definition for "Mutational load" and claim 68 does not require to account accumulated deleterious mutations and calculate a mutation rate based on the definition of "Mutational load", it is unclear how the mutational load of a genomic sample can be measured using the methods recited in claims 68-75 and 80-87, the mutational load of a single region of the genome can be estimated using the method recited in claim 76, the mutational load of a location in step (f) to the same location on the reference sample can be compared using the method recited in claim 77, and the mutational load of locations of the genome in step (f) can be determined using the methods recited in claims 78 and 79. Furthermore, although step f) of claim 68 requires accounting for sequence error during processing comprising identifying tagged nucleic acid molecules that have mutated during the amplification of step c) and ignoring so mutated tagged nucleic acid molecules, since it is known that PCR can cause different false mutations in amplified nucleic acid sequences (eg., see abstract and Tables 2 and 3 from McInerney *et al.,* Molecular Biology International, Article ID 287430, August 17, 2014) and claim 68 does not indicate how to differentiate original mutations in a genomic sample from

false mutations in the amplified tagged nucleic acid molecules generated from the PCR, it is unclear how the mutational load of a genomic sample can be measured using the methods recited in claims 68-75 and 80-87, the mutational load of a single region of the genome can be estimated using the method recited in claim 76, the mutational load of a location in step (f) to the same location on the reference sample can be compared using the method recited in claim 77, and the mutational load of locations of the genome in step (f) can be determined using the methods recited in claims 78 and 79. Since, in order to measure the mutational load of a genomic sample, the skilled artisan is required to at least perform undue experiments to account accumulated deleterious mutations, calculate a mutation rate, and differentiate original mutations in a genomic sample from false mutations in the amplified tagged nucleic acid molecules generated from the PCR, the methods in claims 68-80 and 82-87 is unpredictable.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genentech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "[I]t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In view of above discussions, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to

make the invention as it is claimed. The undue experimentation at least includes to test whether the mutational load of a genomic sample can be measured using the methods recited in claims 68-80 and 82-87.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working example related to claimed invention and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

15. 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.

16. Claims 68-80 and 82-87 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.

17. Claim 68 recites the limitation "the genome sample" in step a). There is insufficient antecedent basis for this limitation in the claim because there is no phrase "a genome sample" before "the genome sample". Please clarify.

18. Claim 68 is rejected as vague and indefinite in view of step b) because it is unclear what means "corresponding to". Does the phrase "a portion corresponding to a segment of the segments of the genomic nucleic acids from step (a) and a portion corresponding to a nucleic acid tag of the nucleic acid tags" mean that "a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags"? Please clarify.

19. Claim 68 is rejected as vague and indefinite in view of step e) because it is unclear that the subsequence associated with the nucleic acids of each of the tag associated sequence read of step (d) is mapped to where. Please clarify.

20. Claim 76 is rejected as vague and indefinite because the claim does not make sense. Does the claim mean "estimating the mutational load of a single region of the genome by assigning the highest mutational load in a location of the single region obtained in step (f) as the mutational load of the single region of the genome"? Please clarify.

21. Claim 82 is rejected as vague and indefinite in view of step i). Since claim 68 or 82 does not require that the nucleic acids from the genome sample is genomic nucleic acids, it is unclear why a polynucleotide tail can be added to the ends of the segments of the genomic nucleic acids. Please clarify.

22. Claim 87 is rejected as vague and indefinite because the claim does not make sense because the tag associated sequence reads should generated from nucleic acid sequences and is not generated from a single species or a single cell. Please clarify.

Conclusion

23. No claim is allowed.

24. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571)272-0731.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
March 26, 2021

Notice of References Cited	Application/Control No. 16/269,818	Applicant(s)/Patent Under Reexamination Hicks et al.	
	Examiner FRANK W LU	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
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	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	"Mutational load". printed on 3/26/2021.
	V	McInerney et al., Error Rate Comparison during Polymerase Chain Reaction by DNA Polymerase. Molecular Biology International, Article ID 287430, August 17, 2014.
	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.

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 5981/81503-AAA/GJG/ADR	Application No. 16/269,818
Information Disclosure Statement by Applicant (Use several sheets if necessary)		First Named Inventor James Hicks	Confirmation Number 8088
(37 CFR §1.98(b))		Filing Date February 7, 2019	Group Art Unit Not yet assigned

U.S. Patent Documents

Examiner Initial	Cite ID[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM/DD/YYYY	First named inventor
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	2	9,487,829	11/8/2016	Vogelstein
	3	9,476,095	10/25/2016	Vogelstein
	4	9,404,156	8/2/2016	Hicks
	5	8,741,606	6/3/2014	Casbon
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	26	2010/0203538	8/12/2010	Dube

Examiner Signature	Date Considered
/FRANK W LU/	03/26/2021

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U.S. Patent Documents

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Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Cite ID[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM/DD/YYYY	Country or Patent Office[3]	Class	T[6]
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	39	WO 2007/062445	6/7/2007	WO		
	40	DE 10 2008 025 656 A1	12/3/2009	DE		

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	41	June 26, 2012 International Search Report issued in connection with PCT International Application No. PCT/US2011/057350 (WO 2012/054873)
	42	April 23, 2013 International Preliminary Report on Patentability issued in connection with PCT International Application No. PCT/US2011/057350 (WO 2012/054873)
	43	February 13, 2014 Extended European Search Report, issued in connection with European Patent Application No. 11835243.4

Examiner Signature	Date Considered
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		Filing Date February 7, 2019	Group Art Unit Not yet assigned

NON PATENT LITERATURE DOCUMENTS		
Examiner Initial	**Cite ID[1]**	**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, page(s), volume-issue number(s), publisher, city and/or country where published.**
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	48	Notice of Opposition to a European Patent, filed January 25, 2019 by Opponent, James Poole Limited, with European Patent Office, concerning European Patent No. EP 2630263
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Examiner Signature	/FRANK W LU/	Date Considered	03/26/2021

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Courtesy Reminder for
Application Serial No: 16/269,818

Attorney Docket No: 81503-AAA/GJG/ADR
Customer Number: 23432
Date of Electronic Notification: 04/01/2021

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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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 16/269,818	Filing Date 02/07/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	10/01/2021	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 16	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

		(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 $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.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/KATARA D SINGLETARY/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

90 Park Avenue
21st Floor
New York, NY 10016
October 1, 2021

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

SECOND INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, applicants direct the Examiner's attention to the following items listed below which are also listed on the Substitute Form PTO-1449 attached hereto as **Exhibit A.**

According to 37 C.F.R. § 1.97(c), a Supplemental Information Disclosure Statement filed after the period specified in 37 C.F.R. § 1.97(b) shall be considered if accompanied by the fee set forth in 37 C.F.R. § 1.17(p) or a statement under 37 C.F.R. § 1.97(e). The fee set forth in 37 C.F.R. § 1.17(p) is ONE HUNDRED THIRTY DOLLARS ($130.00) for a small entity and authorization is hereby given to charge this amount to a credit card linked to Customer Number 1912.

Copies of items **1-11** are attached hereto as **Exhibits 1-11,** respectively.

1. August 20, 2019 Response to Opposition including Main Request and Auxiliary Requests 1-5 filed with the European Patent Office by Patentee Cold Spring Harbor Laboratory in connection with European Patent No. EP 2630263 (**Exhibit 1**);
2. September 26, 2019 Provisional and Non-Binding Opinion of the Opposition Division issued in connection with European Patent No. EP 2630263 (**Exhibit 2**);
3. November 7, 2019 Reply to the Provisional and Non-Binding

Opinion of the Oppositon Division including Corrected Auxiliary Requests 1, 3, and 5 filed with the European Patent Office by Patentee Cold Spring Harbor Laboratory in connection with European Patent No. EP 2630263 (**Exhibit 3**);

4. March 3, 2020 Submissions from the Opponent in accordance with Rule 116 EPC filed by Opponent James Poole Limited in connection with European Patent No. EP 2630263 (**Exhibit 4**);

5. Wang, Tian-Li, et al. "Digital karyotyping." Proceedings of the National Academy of Sciences 99, no. 25 (December 10, 2002): 16156-16161. (**Exhibit 5**);

6. January 15, 2021 Patent Proprietor's final written submissions in accordance with Rule 116 EPC filed in connection with European Patent No. EP 2630263 (**Exhibit 6**);

7. Linnarsson, Sten. "Recent advances in DNA sequencing methods–general principles of sample preparation." Experimental cell research 316, no. 8 (2010): 1339-1343. (**Exhibit 7**);

8. March 17, 2021 Information regarding the result of oral proceedings in connection with European Patent No. EP 2630263 (**Exhibit 8**);

9. May 6, 2021 Interlocutory decision in Opposition proceedings (Art. 101(3)(a) and 106(2) EPC issued by the Opposition Division in connection with European Patent No. EP 2630263 (**Exhibit 9**);

10. May 7, 2021 Office Action issued in connection with Canadian Patent Application No. 3,080,686 (**Exhibit 10**);

11. September 7, 2021 Response to May 7, 2021 Office Action filed in connection with Canadian Patent Application No. 3,080,686 (**Exhibit 11**).

The Examiner is respectfully requested to make of record each item listed on the Form PTO-1449 Substitute by initialing and dating the attached Form PTO-1449 Substitute and returning a copy of the initialed and dated form to applicants' undersigned attorney.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the $130.00 fee set forth in 37 C.F.R. § 1.17(p) is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

Gary J. Gershik
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Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on October 1, 2021.

/Darren Haber/

Darren Haber

AMENDMENTS TO THE SPECIFICATION

Please amend the first paragraph of the specification, found on page 1, lines 4-11 as follows:

> This application is a continuation of U.S. Serial No. 15/063,278, filed March 7, 2016, now U.S. Patent No. 10,947,589, issued February 24, 2021, which is a continuation of U.S. Serial No. 13/278,333, filed October 21, 2011, now U.S. Patent No. 9,404,156, issued August 2, 2013, which claims the benefit of U.S. Provisional Application Nos. 61/510,579, filed July 22, 2011, and 61/406,067, filed October 22, 2010 the contents of each of which are hereby incorporated by reference in their entirety into this application.

REMARKS

In this amendment, applicant has amended claim 68, 72, 75, 81, 82, and 85, cancelled claims 76-80, and added new claim 88. Support for the amendment to claim 68 may be found in the specification, *inter alia*, at page 52, lines 15-21. Claims 68, 72, 75, 81, 82, and 85 have also been amended to improve their wording. Support for new claim 88 may be found in the specification, *inter alia*, at page 66, line 25.

Specification

In the April 1, 2021 Office Action, the Examiner objected to the specification because the first paragraph of the specification should be updated to reflect that U.S. Serial No. 15/063,278 has now issued as a patent.

Applicant's response

In response, applicant has amended the specification as required by the Examiner.

Claim Objections

In the April 1, 2021 Office Action, the Examiner objected to claim 68 because (1) no period should appear after the label of each step, (2) "during processing" in step (f) should be deleted, and (3) "the amplification of step (c) should be "the PCR of step (c)".

The Examiner also objected to claim 72 because "the sequence of individual nucleic acid tags is known prior to generating tagged nucleic acid molecules" should allegedly be "the sequences of the nucleic acid tags are known prior to said generating tagged nucleic acid molecules"

The Examiner also objected to claim 75 because "the tag is" should be "the nucleic acid tags are."

The Examiner also objected to claims 78 and 79 because no period should appear after the label of each step.

The Examiner also objected to claim 78 because: (1) "determining the mutational load of locations of the genome in step (f) which comprise

a first region of the genome" should allegedly be "determining the mutational load of a first region of the genome in step (f)"; (2) "determining the mutational load of locations of the genome in step (f) which comprise a second region of the genome" should allegedly be "determining the mutational load of a second region of the genome in step (f)"; and (3) "is comprised of" should allegedly be "comprises".

The Examiner also objected to claim 79 because (1) "determining the mutational load of the genome in step (f) for the locations on the genome which comprise a third region of the genome" should allegedly be "determining the mutational load of a third region of the genome in step (f)"; (2) "is comprised of" should allegedly be "comprises"; and (3) "obtaining an average of the mutational load determined in step (f) for locations which comprise the second region and the mutational load obtained in step (f) for locations which comprise the third region" should allegedly be "obtaining an average of the mutational load of the mutational load of the second region and the mutational load of the third region".

The Examiner also objected to claim 82 because "such that each tagged nucleic acid molecule is unique, thereby generating each unique tagged nucleic acid molecule" should allegedly be "such that each of the tagged nucleic acid molecule is unique, thereby generating the unique tagged nucleic acid molecules".

Finally, the Examiner objected to claim 85 because "the PCT" should be "the PCR".

Applicant's response

In response, applicant has amended claims 68, 72, 75, 82 and 85 in accordance with the Examiner's suggestions.

Claims 78 and 79 have been cancelled without prejudice or disclaimer. Accordingly, the objections to these claims are now moot.

35 U.S.C. § 112 – Written Description

In the April 1, 2021 Office Action, the Examiner rejected claims 68-80 and 82-87 as allegedly failing to comply with the written description requirement.

The Examiner alleged that acknowledged that the specification describes: "Through sequence error during processing, the tag may very occasionally mutate, creating the appearance of a new tagged nucleic acid molecule. But if the set of tags are sufficiently large, the tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting"

The Examiner also acknowledged that the specification describes: "[T]he above description is of methodology designed to measure copy number and mutational loads throughout much of the genome in single cells"

However, the Examiner alleged that the specification does not describe 1) accounting for sequence error comprising identifying tagged nucleic acid molecules that have mutated during the amplification of step c) and ignoring so mutated tagged nucleic acid molecules; 2) measuring the mutational load of the genomic sample based on the method of claim 68; 3) estimating the mutational load of a single region of the genome; 4) comparing the mutational load of a location in step (f) to the same location on the reference sample, and 5) determining the mutational load of locations of the genome in step (f).

Applicant's response

In response, without conceding the correctness of the Examiner's rejection and solely to advance prosecution, applicant has amended claim 68 and cancelled claims 76-80. Claim 68 has also been amended to no longer recite "mutational load." Accordingly, points 2-5 of the Examiner's rejection noted above are now moot.

With respect to point 1, step f) of claim 68 has been amended to recite "when counting, accounting for sequence error by ignoring

unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome."

Applicant submits that this step is clearly supported by the description at page 52, lines 15-21, acknowledged by the Examiner, which explains: "Through sequence error during processing, the tag may very occasionally mutate, creating the appearance of a new tagged nucleic acid molecule. But if the set of tags are sufficiently large, the tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting."

Accordingly, the Examiner's written description should be withdrawn.

35 U.S.C. § 112 – Enablement

In the April 1, 2021 Office Action, the Examiner rejected claims 68-80 and 82-87 under 35 U.S.C. § 112 as allegedly lacking enablement. The Examiner acknowledged that steps a) to c) of claim 68 are enabled but alleged that the specification does not reasonably provide enablement for measuring the mutational load of a genomic sample using the methods recited in claims 68-80 and 82-87.

Applicant's response

In response, without conceding the correctness of the Examiner's rejection and solely to advance prosecution, applicant has amended claim 68 to no longer recite measuring mutational load. Further, step f) of claim 68 has been amended to recite "when counting, accounting for sequence error by ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome." Applicant submits that a person of ordinary skill in the art could readily identify unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome.

Accordingly, the Examiner's enablement rejection should be withdrawn.

35 U.S.C. § 112 – Indefiniteness

In the April 1, 2021 Office Action, the Examiner rejected claims 68-80 and 82-87 under 35 U.S.C. § 112 as allegedly indefinite.

The Examiner rejected claim 68 for lack of antecedent basis of "the genome sample" in step a), because it is allegedly unclear what "a portion corresponding to" means, and because it is allegedly unclear what the subsequence associated with the nucleic acids is mapped to.

Further, the Examiner rejected claim 76 as allegedly indefinite.

Still further, the Examiner rejected claim 82 because it recites genomic nucleic acids whereas claim 68 and 82 do not recite genomic nucleic acids.

Finally, the Examiner rejected claim 87 because the tag associated sequence reads should be generate from nucleic acids, not from a single species or a single cell.

Applicant's response

In response, applicant has amended step a) of claim 68 to recite "a genomic sample." Further, applicant has amended step b) to no longer recite "a portion corresponding to." Still further, applicant has amended step e) to recite that mapping is "to a location in the genome." Applicant has also amended claim 68 to refer to "unique tagged nucleic acid molecules" in steps c) to f) to more clearly indicate that the tagged nucleic acid molecules of these steps are the "unique tagged nucleic acid molecules" generated in step b). Accordingly, the Examiner's rejection to claim 68 as allegedly indefinite should be reconsidered and withdrawn.

Further, applicant has cancelled claim 76 without prejudice or disclaimer. Accordingly, the Examiner's rejection of this claim is now moot.

Further, applicant has amended claim 82 to recite that the nucleic acids from the genomic sample are genomic nucleic acids.

Finally, applicant has amended claim 87 to recite that the tag associated sequence reads are generated from nucleic acids.

Accordingly, each of the Examiner's indefiniteness rejections have been addressed and should be withdrawn.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the fee of seven hundred forty dollars ($740.00) for a small entity for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

Gary J. Gershik
Registration No. 39,992
Attorney for Applicants
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Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on October 1, 2021.

/Darren Haber/

Darren Haber

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1-67. (Cancelled).

68. (Currently Amended) A method ~~for measuring the mutational load of a genomic sample,~~ comprising:

[[a.]]a) obtaining segments of nucleic acids from ~~the genome~~a genomic sample;

[[b.]]b) tagging the segments with nucleic acid tags, thereby generating unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises ~~a portion corresponding to~~ a segment of the segments of the nucleic acids from step (a) and a ~~portion corresponding to a~~ nucleic acid tag of the nucleic acid tags;

[[c.]]c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified unique tagged nucleic acid molecules;

[[d.]]d) generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c);

[[e.]]e) assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping ~~the subsequence associated with the nucleic acids of~~ each of the tag associated sequence reads of step (d) to a location in the genome; and

[[f.]]f) when counting, accounting for sequence error ~~during processing comprising identifying tagged nucleic acid molecules that have mutated during the amplification of step c) and ignoring so mutated~~ by ignoring unique tagged nucleic acid molecules that differ by a single nucleotide

relative to other unique tagged nucleic acid molecules that map to the same location on the genome.~~,~~

~~thereby measuring the mutational load of the genomic sample~~.

69. (Previously Presented) The method of claim 68, wherein the segments of nucleic acids are selected from any one of the following: genomic nucleic acids, RNA, mRNA transcripts, or cDNA from mRNA transcripts.

70. (Previously Presented) The method of claim 69, further comprising obtaining a genomic profile from the genomic sample, obtaining an expression profile from the genomic sample, or obtaining copy number information from the genomic sample.

71. (Previously Presented) The method of claim 68, wherein the polymerase chain reaction of step c) comprises region specific PCR primers.

72. (Currently Amended) The method of claim 68, wherein the unique tagged nucleic acid molecules differ at more than one nucleotide or wherein the sequences of ~~individual~~ the nucleic acid tags ~~is~~ are known prior to said generating unique tagged nucleic acid molecules.

73. (Previously Presented) The method of claim 69, wherein the segments of the nucleic acids are segments of genomic nucleic acids, and are produced by mechanical shearing, heating, or sonication of the genome sample.

74. (Previously Presented) The method of claim 68, wherein the nucleic acid tags comprise a sample tag or a sample tag set.

75. (Currently Amended) The method of claim 68, wherein the nucleic acid tags are ~~tag is~~ double-stranded.

76-80. (Cancelled)

81. (Withdrawn - Currently Amended) The method of claim 68, wherein said tagging the segments comprises:

i) adding a polynucleotide tail to the ends of the segments of the genomic nucleic acids to generate zero-th order derivative strands comprising the polynucleotide tail;

ii) subjecting the zero-th order derivative strands of step (i) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement of the zero-th order derivative strands, thereby generating first order derivative strands;

iii) adding a polynucleotide tail to the first order derivative strands, thereby generating a first order derivative strands comprising the polynucleotide tail;

iv) subjecting the first order derivative strands comprising the polynucleotide tail to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the first order derivative strands under conditions that promote the formation of only one complement of the first order derivative strands comprising the polynucleotide tail, thereby generating second order derivative strands,

wherein the primers of at least one of steps ii) and iv) comprise nucleic acid tags, such that each tagged nucleic acid molecule is unique, and the first order derivative strands and the second

order derivative strands are the unique tagged nucleic acid molecules.

82. (Currently amended) The method of claim 68, wherein nucleic acids from the genomic sample are genomic nucleic acids, and said tagging the segments comprises:

i) adding a polynucleotide tail to the ends of the segments of genomic nucleic acids, thereby generating zero-th order derivative strands comprising the polynucleotide tail,

ii) subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

iii) subjecting the product of step (ii) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (i) under conditions which promote the formation of only one complement of the product of step (ii), wherein the primers of step (ii) and the primers of step (iii) have different nucleotide sequences, and wherein the polymerase has 3′-5′ proofreading activity,

wherein the primers of at least one of steps (ii) and (iii) comprise nucleic acid tags, such that each of the tagged nucleic acid molecules ~~is~~ are unique, thereby generating ~~each~~ the unique tagged nucleic acid molecules.

83. (Previously Presented) The method of claim 81, wherein said adding the polynucleotide tail comprises the use of a terminal transferase.

84. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to PCR or the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d).

85. (Currently Amended) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to ~~the PCT~~the PCR or prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c).

86. (Previously Presented) The method of claim 85, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads.

87. (Previously Presented) The method of claim 68, wherein the tag associated sequence reads are generated from nucleic acids of: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

88. (New) The method of claim 68, wherein the genomic sample is a blood sample or bone marrow sample.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

90 Park Avenue
21st Floor
New York, NY 10016
October 1, 2021

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO APRIL 1, 2021 OFFICE ACTION AND PETITION FOR THREE-MONTH EXTENSION OF TIME

This Amendment is submitted in response to the April 1, 2021 Office Action issued in connection with the above-identified application. A response to the April 1, 2021 Office Action was originally due July 1, 2021. Applicants hereby petition for a three-month extension of time. The fee for a three-month extension of time is seven hundred forty dollars ($740.00) for a small entity and applicant hereby authorizes the U.S. Patent and Trademark Office to charge this amount to a credit card linked to Customer Number 1912. With a three-month extension of time, a response is now due October 1, 2021. Accordingly, this Amendment is being timely filed.

Amendments to the Specification begin on page **2** of this paper.
Amendments to the Claims begin on page **3** of this paper.
Remarks begin on page **8** of this paper.

Electronic Patent Application Fee Transmittal

Application Number:	16269818
Filing Date:	07-Feb-2019
Title of Invention:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
First Named Inventor/Applicant Name:	James Hicks
Filer:	Gary J. Gershik/Darren Haber
Attorney Docket Number:	81503-AAA/GJG/ADR

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	2253	1	740	740
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	130	130
		Total in USD ($)		**870**

Electronic Acknowledgement Receipt

EFS ID:	43930049
Application Number:	16269818
International Application Number:	
Confirmation Number:	8088
Title of Invention:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
First Named Inventor/Applicant Name:	James Hicks
Customer Number:	23432
Filer:	Gary J. Gershik/Darren Haber
Filer Authorized By:	Gary J. Gershik
Attorney Docket Number:	81503-AAA/GJG/ADR
Receipt Date:	01-OCT-2021
Filing Date:	07-FEB-2019
Time Stamp:	16:32:59
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$870
RAM confirmation Number	E202101G33184029
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

IPR2025-01353
CSHL EX2001

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		211001_81503-AAA_Response_DH.pdf	160523 69aeacaed880051b55ed54f8f6764ccd23464bd7	yes	14
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Specification		2	2	
	Claims		3	7	
	Applicant Arguments/Remarks Made in an Amendment		8	14	
Warnings:					
Information:					
2	Other Reference-Patent/App/Search documents	211001_81503-AAA_IDS2_Exhibit_01_DH.pdf	3788702 1372edc3b3e1536b7995a1f6d6a1e4d0c6417184	no	90
Warnings:					
Information:					
3	Other Reference-Patent/App/Search documents	211001_81503-AAA_IDS2_Exhibit_02_DH.pdf	225747 0408db4e80e2300627c3c2328790a7c8acf2e905	no	4
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Information:					
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Warnings:					
Information:					

5	Other Reference-Patent/App/Search documents	211001_81503-AAA_IDS2_Exhibit_04_DH.pdf	509367 27995d843cd3316bf370474eaaba5fa0faf0fc27	no	8
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Information:					
6	Non Patent Literature	211001_81503-AAA_IDS2_Exhibit_05_DH.pdf	1469636 e3d45647ac66d923d3e1d55defb86983654f462e	no	6
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Information:					
7	Other Reference-Patent/App/Search documents	211001_81503-AAA_IDS2_Exhibit_06_DH.pdf	459736 f9a6e4bc192e2c81b2f4ab5ae94e9c2fa4e75bdd	no	8
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Information:					

12	Other Reference-Patent/App/Search documents	211001_81503-AAA_IDS2_Exhibit_11_DH.pdf	722967 079e5bedc8882a02bab7215b2edcdafd64fb2d6f	no	23
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Information:					
13		211001_81503-AAA_IDS2_DH.pdf	324477 59c1a7b79f2dfaff84d06d044c63b42cbbe6e4b0	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	3
	Information Disclosure Statement (IDS) Form (SB08)	4	4

Warnings:					
Information:					
14	Fee Worksheet (SB06)	fee-info.pdf	40847 05e2d8e63a4fc68e5aae30cbf8f49bc3b7acb3c1	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	17755585		

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.

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 81503-AAA/GJG/DH	Application No. 16/269,818
Information Disclosure Statement by Applicant (Use several sheets if necessary)		First Named Inventor James Hicks	Confirmation Number 8088
(37 CFR §1.98(b))		Filing Date February 7, 2019	Group Art Unit 1634

NON PATENT LITERATURE DOCUMENTS		
Examiner Initial	**Cite ID[1]**	**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, page(s), volume-issue number(s), publisher, city and/or country where published.**
	1	August 20, 2019 Response to Opposition including Main Request and Auxiliary Requests 1-5 filed with the European Patent Office by Patentee Cold Spring Harbor Laboratory in connection with European Patent No. EP 2630263
	2	September 26, 2019 Provisional and Non-Binding Opinion of the Opposition Division issued in connection with European Patent No. EP 2630263
	3	November 7, 2019 Reply to the Provisional and Non-Binding Opinion of the Oppositon Division including Corrected Auxiliary Requests 1, 3, and 5 filed with the European Patent Office by Patentee Cold Spring Harbor Laboratory in connection with European Patent No. EP 2630263
	4	March 3, 2020 Submissions from the Opponent in accordance with Rule 116 EPC filed by Opponent James Poole Limited in connection with European Patent No. EP 2630263
	5	Wang, Tian-Li, et al. "Digital karyotyping." Proceedings of the National Academy of Sciences 99, no. 25 (December 10, 2002): 16156-16161.
	6	January 15, 2021 Patent Proprietor's final written submissions in accordance with Rule 116 EPC filed in connection with European Patent No. EP 2630263
	7	Linnarsson, Sten. "Recent advances in DNA sequencing methods–general principles of sample preparation." Experimental cell research 316, no. 8 (2010): 1339-1343.
	8	March 17, 2021 Information regarding the result of oral proceedings in connection with European Patent No. EP 2630263
	9	May 6, 2021 Interlocutory decision in Opposition proceedings (Art. 101(3)(a) and 106(2) EPC issued by the Opposition Division in connection with European Patent No. EP 2630263
	10	May 7, 2021 Office Action issued in connection with Canadian Patent Application No. 3,080,686
	11	September 7, 2021 Response to May 7, 2021 Office Action filed in connection with Canadian Patent Application No. 3,080,686

Examiner Signature	Date Considered

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Substitute Disclosure Form (PTO-1449)

Second Information Disclosure Statement

EXHIBIT A

```
(FILE 'HOME' ENTERED AT 23:51:54 ON 30 NOV 2021)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH, EMBASE' ENTERED AT 23:53:34 ON
     30 NOV 2021
L1          1725 S TAGGED NUCLEIC ACID OR TAGGED DNA OR TAGGED RNA
L2        447882 S LOCATE OR LOCATING OR ASSIGN OR ASSIGNING
L3       2894237 S GENOME
L4            14 S L1 AND L2 AND L3
L5             6 DUP REM L4 (8 DUPLICATES REMOVED)
L6            19 S L1 AND L2
L7             9 DUP REM L6 (10 DUPLICATES REMOVED)
```

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	1,203	genome same tagged near3 ("nucleic acid" or DNA or RNA)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/11/30 23:46
L5	26	(locate or locating or assign$) near10 tagged near3 ("nucleic acid" or DNA or RNA) same genome	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/11/30 23:46
L6	26	5 AND ((C12Q2535/122 OR C12Q2537/16 OR C12Q1/683 OR C12Q1/6869 OR C12Q2525/155 OR C12Q2525/191 OR C12Q2537/159 OR C12Q2563/179 OR C12Q1/6874 OR C12Q1/6881 OR C12Q1/6886 OR C12Q2600/156 OR G16B25/00).CPC.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2021/11/30 23:50

11/30/2021 11:50:45 PM
C:\Users\flu\Documents\EAST\Workspaces\~auto.02072018.175405.bak.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	Art Unit
	FRANK W LU	1634

CPC - Searched*		
Symbol	Date	Examiner
Update	11/30/2021	/FL/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
Update	11/30/2021	/FL/

US Classification - Searched*			
Class	Subclass	Date	Examiner
Update		11/30/2021	/FL/

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Update (see attached files)	11/30/2021	/FL/

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

/FRANK W LU/ Primary Examiner, Art Unit 1634	November 30, 2021

IPR2025-01353
GSHL 1202001

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 12/06/2021

Gary J. Gershik; John P. White;
Christopher C. Dunham; Paul Teng
90 PARK AVENUE, 21st Fl
NEW YORK, NY 10016

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
12/06/2021	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):

DUSPTO@cooperdunham.com
patcomm-in-grp@cooperdunham.com
pdocketing@cooperdunham.com

Office Action Summary	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	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 10/1/2021.

☐ 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) 68-75 and 81-88 is/are pending in the application.

5a) Of the above claim(s) 81 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68-75 and 82-88 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 2/7/2019 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 10/1/2021.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on October 1, 2021 has been entered. The claims pending in this application are 68-75 and 81-88 wherein claim 81 has been withdrawn due to election of species mailed on August 25, 2020. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on October 1, 2021. Claims 68-75 and 82-88 will be examined.

Claim Objections

2. Claim 68 is objected to because of the following informality: "when counting, accounting" in step f) should be "counting".

3. Claim 82 is objected to because of the following informalities: (1) "nucleic acids" in line 1 should be "the nucleic acids"; (2) "genomic nucleic acids" in step i) should be "the genomic nucleic acids"; and (3) "are unique" in "wherein" phrase should be "is unique".

Appropriate correction is required.

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. New Matter

Claims 68-75 and 82-88 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.

The recitation "ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome" are added to step f) of independent claim 68 and can be read as "ignoring unique tagged nucleic acid molecules that differ by at least one single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome". Although the specification describes that "[T]hrough sequence error during processing, the tag may very occasionally mutate, creating the appearance of a new tagged nucleic acid molecule. But if the set of tags are sufficiently large, the tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting" (see paragraph [0297] of US 20190/153535 A1, which is US publication of this instant case), nowhere in the specification describes such recitation recited in step f) of claim 68 since "tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored" in paragraph [0297] of US 20190/153535 A1 should mean ignoring the tagged nucleic acid molecules which differ at more than one nucleotide and does not mean ignoring unique tagged nucleic acid molecules that differ by at least one single nucleotide.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

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 68-75 and 82-88 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.

8. Claim 68 is rejected as vague and indefinite in view of step f). Since the specification teaches that "[T]hrough sequence error during processing, the tag may very occasionally mutate, creating the appearance of a new tagged nucleic acid molecule. But if the set of tags are sufficiently large, the tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting" (see paragraph [0297] of US 20190/153535 A1, which is US publication of this instant case), the specification indicates that a sequence error in step f) of

the claim is from each tags of tagged nucleic acid molecules. Since step f) does not indicate where a sequence error comes from, one skilled in the art would not understand the metes and bounds of step (f). Furthermore, since the specification and available art has no definition for "genomic sample" in step a), one skilled in the art would not understand the metes and bounds of this term. Please clarify.

9. Claim 87 is rejected as vague and indefinite. Since claim 68 requires generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c), this indicate that the tag associated sequence reads are generated from the amplified unique tagged nucleic acid molecules of step (c). Although claim 87 is dependent on claim 68, since claim 87 requires that the tag associated sequence reads are generated from nucleic acids of: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes, claims 68 and 87 do not correspond each other. Please clarify.

Double Patenting

10. 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 § 2146 *et seq.* 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.

11. Claims 68-75 and 82-88 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No.10,947,589 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claims in this instant application are either anticipated by, or would have been obvious over, the reference claims. See *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); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although claims 68-75 and 82-88 in this instant application are not identical to claims 1-18 of U.S. Patent No.10,947,589 B2, since the content of U.S. Patent No.10,947,589 B2 indicates that the PCR primers can be region specific PCR primers (see column 25), in an embodiment of the methods, segments of the genomic material are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication (see column 12), the nucleic acid tags can be double-stranded (see column 24), the polymerase can be a polymerase having 3' to 5' proofreading activity and in an embodiment of the methods, a polynucleotide tail is added using a terminal transferase (see column 9), and the tagged nucleic acid can generated from a single organism or two or more organisms or a single cell of each organisms or a population of microbes (see column 10), claims 1-18 of U.S. Patent No. 10,947,589 B2 are directed to the same subject matter and fall entirely within the scope of claims 68-75 and 82-88 in this instant application. In other words, claims 68-75 and 82-88 in this instant application are anticipated by claims 1-18 of U.S. Patent No. 10,947,589 B2.

Response to Arguments

12. Applicant's arguments with respect to claims 68-80 and 82-87 have been considered but are moot because the new ground of rejection does not rely on any reference applied in the prior rejection of record for any teaching or matter specifically challenged in the argument.

Conclusion

13. 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.

14. No claim is allowed.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571)272-0731.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
November 30, 2021

Notice of References Cited	Application/Control No. 16/269,818	Applicant(s)/Patent Under Reexamination Hicks et al.	
	Examiner FRANK W LU	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-10947589-B2	03-2021	Hicks; James	C12Q1/683	1/1
	B					
	C					
	D					
	E					
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	G					
	H					
	I					
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	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	
	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.

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 81503-AAA/GJG/DH	Application No. 16/269,818
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		First Named Inventor James Hicks	Confirmation Number 8088
		Filing Date February 7, 2019	Group Art Unit 1634

NON PATENT LITERATURE DOCUMENTS		
Examiner Initial	**Cite ID[1]**	**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, page(s), volume-issue number(s), publisher, city and/or country where published.**
	1	August 20, 2019 Response to Opposition including Main Request and Auxiliary Requests 1-5 filed with the European Patent Office by Patentee Cold Spring Harbor Laboratory in connection with European Patent No. EP 2630263
	2	September 26, 2019 Provisional and Non-Binding Opinion of the Opposition Division issued in connection with European Patent No. EP 2630263
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	9	May 6, 2021 Interlocutory decision in Opposition proceedings (Art. 101(3)(a) and 106(2) EPC issued by the Opposition Division in connection with European Patent No. EP 2630263
	10	May 7, 2021 Office Action issued in connection with Canadian Patent Application No. 3,080,686
	11	September 7, 2021 Response to May 7, 2021 Office Action filed in connection with Canadian Patent Application No. 3,080,686

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /F.W.L/

Examiner Signature	Date Considered
/FRANK W LU/	12/01/2021

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Substitute Disclosure Form (PTO-1449)

Second Information Disclosure Statement

EXHIBIT A

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Courtesy Reminder for
Application Serial No: 16/269,818

Attorney Docket No: 81503-AAA/GJG/ADR
Customer Number: 23432
Date of Electronic Notification: 12/06/2021

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IPR2025-01353
CSHL EX2001

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/269,818	Filing Date 02/07/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	06/06/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 15	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

		(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 $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".	/TINA J BARDEN/
*** 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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Electronic Patent Application Fee Transmittal

Application Number:	16269818
Filing Date:	07-Feb-2019
Title of Invention:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
First Named Inventor/Applicant Name:	James Hicks
Filer:	Gary J. Gershik/Darren Haber
Attorney Docket Number:	81503-AAA/GJG/ADR

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	740	740
Miscellaneous:				
RCE- 1ST REQUEST	2801	1	680	680
		Total in USD ($)		**1490**

REMARKS

In this amendment, applicant has amended claims 68, 70, 73, 82, and 87. Applicant has also cancelled claim 69 without prejudice or disclaimer. Claims 68, 70, 73, 82, and 87 are amended simply for improved clarity and applicants submit that these amendments do not introduce new matter.

Claim Objections

In the December 6, 2021 Office Action, the Examiner objected to claims 68 and 82. The Examiner alleged that "when counting" in step f) of claim 68 should be "counting." The Examiner further alleged that in claim 82, "nucleic acids" in claim 82 should be "the nucleic acids"; "genomic nucleic acids" should be "the genomic nucleic acids"; and "are unique" in the wherein clause should be "is unique."

Applicant's response

In response, applicant has amended claims 68 and 82. Claim 68 has been amended to recite "obtaining a count of the number of unique tagged nucleic acid molecules that have been assigned to the same location in the genome," consistent with the Examiner's suggestion. Claim 82 has been amended to recite "the genomic nucleic acids" and "is unique" as suggested by the Examiner. Accordingly, the objections to the claims should be reconsidered and withdrawn.

35 U.S.C. § 112 – Written Description (New Matter)

In the December 6, 2021 Office Action, the Examiner rejected claims 68-75 and 82-88 as allegedly failing to comply with the written description requirement.

The Examiner first alleged that "ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome" can be read as "ignoring unique tagged nucleic molecules that differ by at least one single nucleotide relative to other unique

tagged nucleic acid molecules that map to the same location on the genome."

The Examiner acknowledged that the specification describes that "[T]hrough sequence error during processing, the tag may very occasionally mutate, creating the appearance of a new tagged nucleic acid molecule. But if the set of tags are sufficiently large, the tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting."

However, the Examiner alleged that the description in the specification "should mean ignoring the tagged nucleic acid molecules which differ at more than one nucleotide and does not mean ignoring unique tagged nucleic acid molecules that differ by at least one single nucleotide." December 6, 2021 Final Office Action, page 3.

Applicant's response

In response, applicants respectfully traverse the Examiner's rejection.

As acknowledged by the Examiner, the specification explicitly describes ignoring "tagged nucleic acid molecules that differ by a single nucleotide" when counting. Specification as filed, page 54, lines 19-23. A person of skill in the art would understand that tagged nucleic acid molecules that differ by only a single nucleotide map to the same location on the genome. Accordingly, the recitation of "ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome" is supported by page 54, lines 19-23 of the specification and is not new matter.

Accordingly, the Examiner's written description should be withdrawn.

35 U.S.C. § 112 – Indefiniteness

In the December 6, 2021 Office Action, the Examiner rejected claims 68-75 and 82-88 under 35 U.S.C. § 112 as allegedly indefinite.

The Examiner rejected claim 68 as vague and indefinite in view of step f). The Examiner alleged that the specification indicates that a sequence error in step f) of the claim is from each tag of the tagged nucleic acid molecules. However, step f) of the claim does not indicate where a sequence error comes from. On this basis, the Examiner alleged that a Person of Ordinary Skill in the Art (POSA) would not understand the metes and bounds of step f).

Further, the Examiner alleged that "genomic sample" recited in step a) is not defined and a POSA would not understand the metes and bounds of this term.

Finally, the Examiner alleged that claim 87 is vague and indefinite because claim 87 requires the tag associated sequence reads to be generated from nucleic acids of: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes" whereas claim 68 (from which claim 87 depends) requires that the tag associated sequence reads are generated from the amplified unique tagged nucleic acid molecules of step (c).

Applicant's response

In response, applicant respectfully traverses the Examiner's rejection.

First, with respect to step f), although the description in the specification identifies a potential reason to ignore certain tagged nucleic acid molecules during the counting step (i.e. "the tag may very occasionally mutate" Specification as filed, page 54, lines 17-18"), the specification ***also*** explicitly describes that "tagged nucleic acid molecules that differ by a single nucleotide can [] be ignored when counting." Specification as filed, page 54, lines 19-23. A person of skill in the art would understand that tagged nucleic acid molecules that differ by only a single nucleotide map to the same location on the genome. Accordingly, metes and bounds are clear for the step of "ignoring unique tagged nucleic acid molecules that differ by a single

nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome".

Regarding the recitation of "genomic sample" in claim 68, without conceding the correctness of the rejection and solely to advance prosecution, applicant has amended claims 68 to recite "genomic nucleic acids from a sample." Claims 70, 73, 82, and 88 have been amended to be consistent with the recitation of "genomic nucleic acids from a sample" in claim 68. Accordingly, this rejection should be reconsidered and withdrawn.

Regarding the rejection of claim 87, without conceding the correctness of the rejection and solely to advance prosecution, applicant has amended the claim to clarify that the nucleic acids originate from a single species, a single cell, two or more organisms, two or more species, or from a population of microbes. Accordingly, this recitation is consistent with part (c) of claim 68.

Double Patenting

In the December 6, 2021 Final Office Action, the Examiner rejected claims 68-75 and 82-88 under nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 10,947,589 B2. The Examiner acknowledged that the claims are not identical, but alleged that they are not patentably distinct from each other.

Applicant's response

In response, applicant will consider filing a Terminal Disclaimer over the cited patents and applications once the claims are found to be otherwise patentable.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the fee of seven hundred forty dollars ($740.00) for a small entity for a three-month extension of time, the fee of six hundred and eighty dollars ($680.00) for a Request for Continued Examination (RCE), and the processing fee of one hundred and forty dollars ($140.00) for requesting a suspension of action, are deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

_____

Gary J. Gershik
Registration No. 39,992
Attorney for Applicants
Amster, Rothstein & Ebenstein LLP
90 Park Avenue, 21st Floor
New York, NY 10016
(212) 336-8000

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on June 6, 2022.

/Darren Haber/

_____
Darren Haber

PTO/SB/30EFS (07-09)
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	16/269,818	Filing Date	2019-02-17	Docket Number (if applicable)	81503-AAA/GJG/DH	Art Unit	2634
First Named Inventor	James Hicks			Examiner Name	Frank Lu		

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 3
(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

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	/Gary J. Gershik/	Date (YYYY-MM-DD)	2022-06-06
Name	Gary J. Gershik	Registration Number	39992

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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:

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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.

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 Acknowledgement Receipt

EFS ID:	45885045
Application Number:	16269818
International Application Number:	
Confirmation Number:	8088
Title of Invention:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION
First Named Inventor/Applicant Name:	James Hicks
Customer Number:	23432
Filer:	Gary J. Gershik/Darren Haber
Filer Authorized By:	Gary J. Gershik
Attorney Docket Number:	81503-AAA/GJG/ADR
Receipt Date:	06-JUN-2022
Filing Date:	07-FEB-2019
Time Stamp:	15:45:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1490
RAM confirmation Number	E202266F46011865
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

IPR2025-01353
CSHL EX2001

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		220606_81503-AAA_Amendment_DH.pdf	213098 d8e0a86c438ad0a24e9e11c892ab323d8453a42f	yes	11
	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	6	
	Applicant Arguments/Remarks Made in an Amendment		7	11	
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	220606_81503-AAA_RCE_DH.pdf	799232 1f5368a9f3ea0d68a891119e0aab2f92e59f4969	no	3
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	43233 b29413820e2bcd2d54cabd1c8fa8b53eae636f44	no	2
Warnings:					
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		Total Files Size (in bytes):	1055563		

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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.

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1-67. (Cancelled).

68. (Currently Amended) A method comprising:

a) obtaining segments of genomic nucleic acids from a ~~genomic~~ sample;

b) tagging the segments with nucleic acid tags, thereby generating unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;

c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified unique tagged nucleic acid molecules;

d) generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c);

e) assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and

f) ~~when counting~~obtaining a count of the number of unique tagged nucleic acid molecules that have been assigned to the same location in the genome, accounting for sequence error by ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome.

69. (Cancelled).

70. (Currently Amended) The method of claim 69, further comprising obtaining a genomic profile from the ~~genomic~~ sample, obtaining an expression profile from the ~~genomic~~ sample, or obtaining copy number information from the ~~genomic~~ sample.

71. (Previously Presented) The method of claim 68, wherein the polymerase chain reaction of step c) comprises region specific PCR primers.

72. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules differ at more than one nucleotide or wherein the sequences of the nucleic acid tags are known prior to said generating unique tagged nucleic acid molecules.

73. (Currently Amended) The method of claim 69, wherein the segments of the genomic nucleic acids ~~are segments of genomic nucleic acids, and~~ are produced by mechanical shearing, heating, or sonication of the ~~genome~~ sample.

74. (Previously Presented) The method of claim 68, wherein the nucleic acid tags comprise a sample tag or a sample tag set.

75. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are double-stranded.

76-80. (Cancelled)

81. (Withdrawn) The method of claim 68, wherein said tagging the segments comprises:

i) adding a polynucleotide tail to the ends of the segments of the genomic nucleic acids to generate zero-th order derivative strands comprising the polynucleotide tail;

ii) subjecting the zero-th order derivative strands of step (i) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands under conditions that promote the formation of only one complement of the zero-th order derivative strands, thereby generating first order derivative strands;

iii) adding a polynucleotide tail to the first order derivative strands, thereby generating a first order derivative strands comprising the polynucleotide tail;

iv) subjecting the first order derivative strands comprising the polynucleotide tail to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the first order derivative strands under conditions that promote the formation of only one complement of the first order derivative strands comprising the polynucleotide tail, thereby generating second order derivative strands,

wherein the primers of at least one of steps ii) and iv) comprise nucleic acid tags, such that each tagged nucleic acid molecule is unique, and the first order derivative strands and the second order derivative strands are the unique tagged nucleic acid molecules.

82. (Currently amended) The method of claim 68, wherein ~~nucleic acids from the genomic sample are genomic nucleic acids, and~~ said tagging the segments comprises:

i) adding a polynucleotide tail to the ends of the segments of the genomic nucleic acids, thereby generating zero-th order derivative strands comprising the polynucleotide tail,

ii) subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

iii) subjecting the product of step (ii) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (i) under conditions which promote the formation of only one complement of the product of step (ii), wherein the primers of step (ii) and the primers of step (iii) have different nucleotide sequences, and wherein the polymerase has 3′-5′ proofreading activity,

wherein the primers of at least one of steps (ii) and (iii) comprise nucleic acid tags, such that each of the tagged nucleic acid molecules ~~are unique~~ is unique, thereby generating the unique tagged nucleic acid molecules.

83. (Previously Presented) The method of claim 81, wherein said adding the polynucleotide tail comprises the use of a terminal transferase.

84. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to PCR or the amplified tagged nucleic acid molecules

produced in step (c) are subjected to hybrid capture prior to step (d).

85. (Previously Presented) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR or prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c).

86. (Previously Presented) The method of claim 85, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads.

87. (Currently Amended) The method of claim 68, wherein the tag associated sequence reads are generated from nucleic acids originating from~~acids of~~: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

88. (Currently Amended) The method of claim 68, wherein the ~~genomic~~ sample is a blood sample or bone marrow sample.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

90 Park Avenue
21st Floor
New York, NY 10016
June 6, 2022

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO DECEMBER 6, 2021 FINAL OFFICE ACTION AS A SUBMISSION ACCOMPANYING A REQUEST FOR CONTINUED EXAMINATION (RCE), AND PETITION FOR THREE-MONTH EXTENSION OF TIME

This Amendment is a submission under 37 6C.F.R. §1.114 accompanying a Request for Continued Examination (RCE) and responds to the issues raised in a December 6, 2021 Final Office Action issued in connection with the above-identified application. A response to the December 6, 2021 Office Action was originally due March 6, 2022. Applicants hereby petition for a three-month extension of time. The fee for a three-month extension of time is seven hundred forty dollars ($740.00) for a small entity and authorization is hereby given to charge this amount to a credit card linked to Customer Number 1912. With a three-month extension of time, a response is now due June 6, 2022. Accordingly, this Amendment and the RCE for which it accompanies is being timely filed.

Amendments to the Claims begin on page **2** of this paper.
Remarks begin on page **7** of this paper.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 06/14/2022

Gary J. Gershik; John P. White;
Christopher C. Dunham; Paul Teng
90 PARK AVENUE, 21st Fl
NEW YORK, NY 10016

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/14/2022

Please find below and/or attached an Office communication concerning this application or proceeding.

The request for deferral/suspension of action under 37 CFR 1.103 has been approved.

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
16/269,818	02/07/2019	Hicks et al.	81503-AAA/GJG/ AD

Gary J. Gershik; John P. White; Christopher C. Dunham; Paul Teng
90 PARK AVENUE, 21st Fl
NEW YORK, NY 10016

EXAMINER	
LU, FRANK	
ART UNIT	**PAPER**
1634	20220610

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

The request for deferral/suspension of action under 37 CFR 1.103 has been approved.

/TINA J BARDEN/ LIE, OCDD	571-272-0555

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L465	0	(tag OR linker OR adaptor OR adapter) SAME genomic SAME (amplify OR amplifying OR amplification OR PCR) SAME sequence NEAR read SAME (assign OR assigning OR assignment) near5 location SAME sequence NEAR error	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/10/22 11:29 PM
L466	8	(tag OR linker OR adaptor OR adapter) SAME genomic SAME (amplify OR amplifying OR amplification OR PCR) SAME sequence NEAR read SAME (assign OR assigning OR assignment) near5 location	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/10/22 11:30 PM
L467	0	(tag OR linker OR adaptor OR adapter) SAME genomic SAME (amplify OR amplifying OR amplification OR PCR) SAME (assign OR assigning OR assignment) near5 location SAME sequence NEAR error	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/10/22 11:32 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

IPR2025-01353
GSHL EX2001

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	Art Unit
	FRANK W LU	1634

CPC - Searched*		
Symbol	Date	Examiner
Update	10/22/2022	/FL/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
Update	10/22/2022	/FL/

US Classification - Searched*			
Class	Subclass	Date	Examiner
Update		10/22/2022	/FL/

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Update (see attached file)	10/22/2022	/FL/

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

/FRANK W LU/ Primary Examiner, Art Unit 1634	October 22, 2022

IPR2025-01353
GSK-2002001

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 10/27/2022

Gary J. Gershik; John P. White;
Christopher C. Dunham; Paul Teng
90 PARK AVENUE, 21st Fl
NEW YORK, NY 10016

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
10/27/2022	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):

PTODOCKET@ARELAW.COM
klees@ARELAW.com
patcomm-in-grp@cooperdunham.com

Office Action Summary	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	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 6/6/2022.

☐ 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) 68,70-75 and 81-88 is/are pending in the application.

5a) Of the above claim(s) 81 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68,70-75 and 82-88 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 2/7/2019 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

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

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 of RCE and the amendment filed on June 6, 2022 have been entered. The claims pending in this application are claims 68, 70-75, and 81-88 wherein claim 81 has been withdrawn due to the restriction requirement mailed on August 25, 2020. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on June 6, 2022. Claims 68, 70-75, and 82-88 will be examined.

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 68, 70-75, and 82-88 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.

4. Claim 68 is rejected as vague and indefinite in view of step f). Since the specification teaches that "[T]hrough sequence error during processing, the tag may very occasionally mutate, creating the appearance of a new tagged nucleic acid molecule. But if the set of tags are sufficiently large, the tagged nucleic acid molecules will generally differ at more than one nucleotide, and so tagged nucleic acid molecules that differ by a single nucleotide can (optionally) be ignored when counting" (see paragraph [0297] of US 20190/153535 A1, which is US publication of this instant case), the specification indicates that a sequence error in step f) of the claim is from each tags of tagged nucleic acid molecules. Since step f) does not indicate how sequence error can be counted by ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome, one skilled in the art would not understand the metes and bounds of step (f). Does the phrase "counting for sequence error by ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome" in step f) means "avoiding sequence errors by ignoring single nucleotide mutants of the unique tagged nucleic acid molecules that map to the same location on the genome". Please clarify.

5. Claim 87 is rejected as vague and indefinite. Since claim 68 requires generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c), this indicate that the tag associated sequence reads are generated from the amplified unique tagged nucleic acid molecules of step (c). Although claim 87 is dependent on claim 68, since claim 87 requires that the tag associated sequence reads are generated from nucleic acids originating from: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes, claims 68 and 87 do not correspond each other. Please clarify.

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 § 2146 *et seq.* 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 68, 70-75 and 82-88 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No.10,947,589 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the examined claims in this instant application are either anticipated by, or would have been obvious over, the reference claims. See *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); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). Although claims 68-75 and 82-88 in this instant application are not identical to claims 1-18 of U.S. Patent No.10,947,589 B2, since the content of U.S. Patent No.10,947,589 B2 indicates that the PCR primers can be region specific PCR primers (see column 25), in an embodiment of the methods, segments of the genomic material are produced by restriction endonuclease digestion, mechanical shearing, heating, or sonication (see column 12), the nucleic acid tags can be double-stranded (see column 24), the polymerase can be a polymerase having 3' to 5' proofreading activity and in an embodiment of the methods, a polynucleotide tail is added using a terminal transferase (see column 9), and the tagged nucleic acid can generated from a single organism or two or more organisms or a single cell of each organisms or a population of microbes (see column 10), claims 1-18 of U.S. Patent No. 10,947,589 B2 are directed to the same subject matter and fall entirely within the scope of claims 68, 70-75 and 82-88 in this instant application. In other words, claims

68, 70-75 and 82-88 in this instant application are anticipated by claims 1-18 of U.S. Patent No. 10,947,589 B2.

Response to Arguments

In page 10, last paragraph of applicant's remarks, applicant argues that "applicant will consider filing a Terminal Disclaimer over the cited patents and applications once the claims are found to be otherwise patentable".

The above argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because applicant has not filed a terminal disclaimer yet.

Conclusion

8. No claim is allowed.

9. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571)272-0731.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
October 22, 2022

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Cold Spring Harbor Laboratory

U.S. Serial No. : 16/269,818 Examiner : Frank Lu

Filing Date : February 7, 2019 Art Unit : 1634

Confirmation No. : 8088

For : VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

405 Lexington Avenue
48th Floor
New York, NY 10174
April 25, 2023

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

COMMUNICATION FORWARDING POWER OF ATTORNEY BY APPLICANT

Applicant submits herewith, pursuant to 37 C.F.R. § 1.32(d), a Power of Attorney by Applicant, signed on behalf of the Applicant, Cold Spring Harbor Laboratory in connection with U.S. Serial No. 15/063,278, the parent of the subject application.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

Gary J. Gershik
Registration No. 39,992
Attorney for Applicants
Amster, Rothstein & Ebenstein LLP
90 Park Avenue, 21st Floor
New York, NY 10016
(212) 336-8000

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on April 25, 2023.

/Darren Haber/

Darren Haber

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	James Hicks et al.	
U.S. Serial No.	:	15/063,278	Examiner: Frank W. M. Lu
Filing Date	:	March 7, 2016	Art Unit: 1634
Confirmation No.	:	4030	
For	:	VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION	

30 Rockefeller Plaza
20th Floor
New York, New York 10112

BY EFS
Commissioner for Patents
Alexandria, VA

POWER OF ATTORNEY FROM ASSIGNEE
AND STATEMENT UNDER 37 C.F.R. § 3.73(b)

I hereby appoint pursuant to 37 C.F.R. § 3.73(b) the practitioners named below (and revoke any previous powers of attorney given) in connection with the subject application:

Name	Registration No.
John P. White	Reg. No. 28,678
Gary J. Gershik	Reg. No. 39,992
Norman H. Zivin	Reg. No. 25,385
Paul Teng	Reg. No. 40,837
Robert T. Maldonado	Reg. No. 38,232
Tonia A. Sayour	Reg. No. 58,404
Christopher C. Dunham	Reg. No. 22,031

as attorneys to represent the assignee identified below before the United States Patent and Trademark Office (USPTO) in connection with the subject application assigned to the assignee, as evidenced by the USPTO assignment records or assignment document(s) attached to this form in accordance with 37 C.F.R. § 3.73(b).

Please address all communications and direct all telephone calls regarding this application to:

GARY J. GERSHIK, ESQ.
COOPER & DUNHAM LLP
(CUSTOMER NUMBER 23432)
30 ROCKEFELLER PLAZA
NEW YORK, NEW YORK 10112
TEL. (212)278-0400

Cold Spring Harbor Laboratory, having a principal place of business at One Bungtown Road, Cold Spring Harbor, New York 11724, U.S.A., is the assignee of the entire right, title and interest in the subject application by virtue of an assignment, from James Hicks, Nicholas Navin, Jennifer Troge, Zihua Wang, and Michael Wigler to Cold Spring Harbor Laboratory of U.S. Serial No. 13/278,333, filed October 11, 2011, the parent of the subject application, which assignment was recorded with the U.S. Patent and Trademark Office in connection with the parent application on January 16, 2012 at Reel No. 027537, Frame 0950-0955. A copy of the recorded assignment is attached hereto as **Exhibit A**. The subject application is a continuation of U.S. Serial No. 13/278,333, and the attached assignment expressly refers to continuation applications. I am an official authorized to sign this Power Of Attorney on behalf of the assignee.

Date: 4/17/2019

Cold Spring Harbor Laboratory

By: _____

Vladimir Drozdoff, Ph.D., J.D.
Chief Patent Counsel
Office of Technology Transfer
Cold Spring Harbor Laboratory

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 #
16/269,818	**04/25/2023 10:04:42 PM ET**	**81503-AAA/GJG/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	61984930	FILING DATE	02/07/2019
CUSTOMER #	23432	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
230425_81503-AAA_CommFwdPoA_DH.pdf	1	Transmittal Letter	87 KB
230425_81503-AAA_PoA_DH.pdf	2	Power of Attorney	178 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
230425_81503-AAA_CommFwdPoA_DH.pdf	7BB3E27EC304BDEC79DBE2828B27BDCE6583F2D9383BFC9D2BF0C2DE4EB04A3200F78CF95C51F6F71748152EE[illegible]

A470FFB0DE325C8957BC50AA9D00E1E

230425_81503-AAA_PoA_DH.pdf	40907A4A3C8BCEDFEF1E9A3C57E02063FDB97AEEE58539E9898E624DD244D6EE369BED5CA9F56CEE0E5EDFD74849E94ED4A32E8583BD25F22889174F4A7510E9

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/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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/269,818	Filing Date 02/07/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	04/27/2023	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 47	Minus	** 20	= 27		x $40 =	1080
	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	1080

		(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 $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".	/MARQUITA D JONES/
*** 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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REMARKS

In this amendment, applicant has amended claims 68, 73, 82, and 87, cancelled claim 70 and 81, and added new dependent claims 89-122. Claim 68 has been amended to remove the portion of step f) that previously recited "accounting for sequence error…" and to specifically recite "obtaining copy number information". Claims 73 and 82 have been amended to correct their dependency. Claim 87 has been amended to improve its clarity.

Upon entry of this Amendment, a total of 47 claims will be pending. The fee for presenting 27 claims in excess of 20 is $1,080.00 and this fee is being paid via EFS.

Support for the new claims may be found in the subject specification as filed, *inter alia*, as follows:

Claim	**Support in Specification**
89, 106	Page 45, lines 7-10; Page 49, lines 23-26
90, 107	Page 39, lines 8-11
91, 108	Page 39, lines 8-11 and page 31, lines 17-18
92, 109	Page 31, lines 15-16
93, 110	Page 39, lines 9-10
94, 111	Page 48, lines 9-10
95, 112	Page 48, lines 6-7
96, 113	Page 48, lines 7-8
97, 114	Page 48, lines 7-8
98, 115	Page 48, lines 31-32
99, 116	Page 48, lines 31-32
100, 117	Page 49, lines 1-3
101, 118	Page 49, lines 1-3
102, 119	Page 48, lines 24-25
103, 120	Page 48, line 32 to page 49, line 1
104, 121, 122	Page 49, lines 3-7
105	Page 45, lines 15-17

35 U.S.C. § 112 – Indefiniteness

In the October 27, 2022 Office Action, the Examiner rejected claims 68-75 and 82-88 under 35 U.S.C. § 112 as allegedly indefinite. Specifically, the Examiner alleged that step f) in claim 68 renders the claim indefinite because it is allegedly unclear how sequence error can be accounted for by ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location of the genome.

The Examiner further alleged that claim 87 is indefinite because claim 68 requires generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c) whereas claim 87 requires that the tag associated sequence reads are generated from nucleic acids originating from: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

Applicant's response

In response applicant has amended claim 68 to remove the recitation of "accounting for sequence error …" from step f) of claim 68. As discussed during the April 24, 2023 Examiner Interview summarized herein, the rejection of claim 68 and the claims dependent thereon is now moot.

Further, applicant has amended claim 87 to clarify that the unique tagged nucleic acid molecules are generated from genomic nucleic acids originating from: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes. Accordingly, the rejection of claim 87 should be reconsidered and withdrawn.

Double Patenting

In the October 27, 2022 Office Action, the Examiner rejected claims 68-75 and 82-88 under nonstatutory double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 10,947,589 B2. The

Examiner acknowledged that the claims are not identical, but alleged that they are not patentably distinct from each other.

Applicant's response

In response applicants submit herewith, as **Exhibit 1**, a Terminal Disclaimer signed by an authorized official of the assignee of record of U.S. Patent Nos. 9,404,156 and 10,947,589, and of the subject application, namely Cold Spring Harbor Laboratory.

Although U.S. Patent No. 9,404,156 was not included in the Examiner's double-patenting rejection, applicants are including such patent in the Terminal Disclaimer to expedite prosecution by obviating any further potential double patenting rejections.

Under 37 C.F.R. § 1.321(c), a Terminal Disclaimer must be accompanied by the fee set forth in 37 C.F.R. § 1.20(d). Under 37 C.F.R. § 1.20(d), the fee for filing a Terminal Disclaimer is ONE HUNDRED SEVENTY DOLLARS ($170.00). This fee is being paid via EFS.

In accordance with pre-AIA 37 C.F.R. § 1.321(b), the Terminal Disclaimer submitted herewith as **Exhibit 1:** (1) is signed by the assignee of record of the entire interest of the subject application, (2) specifies the portion of the term of patent being disclaimed, (3) states the present extent of assignee's ownership interest in the patent to be granted, and (4) is accompanied by the fee set forth in 37 C.F.R. § 1.20(d). Accordingly, the Terminal Disclaimer submitted herewith complies with the requirements of pre-AIA 37 C.F.R. § 1.321(b).

Applicants understand that there is a requirement to comply with pre-AIA 37 C.F.R. § 3.73(b) in order to satisfy pre-AIA 37 C.F.R. § 1.321. Pre-AIA 37 C.F.R. § 3.73(b) provides that the establishment of ownership by the assignee may be combined with the paper that requests or takes the action. In accordance with pre-AIA 37 C.F.R. § 3.73(b)(1), the Terminal Disclaimer establishes ownership of the subject application by providing (i) Documentary evidence of a chain of title from the original owner to the assignee (e.g., copy of an executed

assignment); and (ii) by specifying where documentary evidence of a chain of title from the original owner to the assignee is recorded in the assignment records of the Office (e.g., reel and frame number).

Additionally, applicant attaches hereto as **Exhibit 2** a statement under 37 C.F.R. § 3.73(c). Both the Statement under 37 C.F.R. § 3.73(c) and the Terminal Disclaimer establish that Cold Spring Harbor Laboratory is assignee of the entire right, title, and interest in the above-identified application pursuant to 37 C.F.R. § 3.73(c). As assignee of the above-identified application, Cold Spring Harbor Laboratory is entitled to conduct prosecution of the subject application as applicant pursuant to 37 C.F.R. § 3.71.

Based on the submission of the Terminal Disclaimer, the double patenting rejection set forth in the October 27, 2022 Office Action has been overcome. Accordingly, applicants respectfully request withdrawal of this rejection.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the fee of five hundred ninety two dollars ($592.00) for a small entity for a three-month extension of time, the fee of one hundred seventy dollars ($170.00) for submission of a Terminal Disclaimer, and the fee of one thousand eighty dollars ($1,080.00) for presenting 27 claims in excess of 20, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

Gary J. Gershik
Registration No. 39,992
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(212) 336-8000

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on April 27, 2023.

/Darren Haber/

Darren Haber

PTO/AIA/96 (08 12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Cold Spring Harbor Laboratory

Application No./Patent No.: 16/269,818 Filed/Issue Date: February 7, 2019

Titled: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Cold Spring Harbor Laboratory, a non-profit research institution

(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 027537, Frame 0950-0955, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

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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IPR2025-01353
Exhibit 2
CSHL EX2001

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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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.

/Gary J. Gershik/	April 27, 2023
Signature	Date
Gary J. Gershik	39,992
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.
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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	04/27/2023 03:19:34 PM ET	81503-AAA/GJG/ADR

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	61997511	AUTHORIZED BY	Gary Gershik
CUSTOMER #	23432	FILING DATE	02/07/2019
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	James Hicks

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 1036	E20234QF20315800	Darren Haber

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2253	EXTENSION FOR RESPONSE WITHIN THIRD MONTH -	592.00	1	592.00
2202	EACH CLAIM IN EXCESS OF 20	40.00	27	1080.00
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
			TOTAL AMOUNT:	$1,842.00

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

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.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

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CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 6

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
230427_81503-AAA_Amendment_DH.pdf		14	-	156 KB
230427_81503-AAA_Amendment_DH-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	92 KB
230427_81503-AAA_Amendment_DH-CLM.pdf	(2-8)	7	Claims	107 KB
230427_81503-AAA_Amendment_DH-INTRVIEW.APP.pdf	(9-9)	1	Applicant summary of interview with examiner	92 KB

230427_81503-AAA_Amendment_DH-REM.pdf	(10-14)	5	Applicant Arguments/Remarks Made in an Amendment	130 KB
230427_81503-AAA_Amendment_Exh2_373_DH.pdf		3	Assignee showing of ownership per 37 CFR 3.73	93 KB
230427_81503-AAA_Amendment_Exh1_TerminalDisclaimer_DH.pdf		8	Terminal Disclaimer Filed	623 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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.

SUMMARY OF APRIL 24, 2023 EXAMINER INTERVIEW

On April 24, 2023, an Examiner Interview was conducted between Examiner Frank Lu and the undersigned, Gary Gershik.

During the interview, the undersigned indicated that applicant was considering amending step f) of claim 68 to remove the portion that recites "accounting for sequence error…", and inquired whether such an amendment would address the indefiniteness rejection of the claims. The Examiner indicated that amending the claim as discussed would address the indefiniteness rejection set forth in the October 27, 2022 Office Action. The Examiner also noted that filing of a Terminal Disclaimer would address the nonstatutory double patenting rejection in the October 27, 2022 Office Action.

Finally, the Examiner stated that he would contact the undersigned if any further issues with the claims remain after an Amendment in response to the October 27, 2022 Office Action is filed.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
Inventor(s)	: James Hicks et al.		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

405 Lexington Avenue
48th Floor
New York, NY 10174

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER

Cold Spring Harbor Laboratory, One Bungtown Road, Cold Spring Harbor, New York 11724, U.S.A., is the owner of (assignee of record of the entire right, title and interest in) the above-identified application by virtue of an assignment of U.S. Serial No. 13/278,333, filed October 21, 2011 the grandparent of the above-identified application, which assignment was recorded with the U.S. Patent and Trademark Office in connection with U.S. Serial No. 13/278,333 on January 16, 2012 at Reel No. 027537, Frame 0950-0955. A copy of the recorded assignment is attached hereto as **Exhibit A**. The subject application, U.S. Serial No. 16/269,818, is a continuation of U.S. Serial No. 15/063,278, filed March 7, 2016, which is a continuation of U.S. Serial No. 13/278,333, filed October 21, 2011. Since the Assignment of rights attached hereto as **Exhibit A** refers to U.S. Serial No. 13/278,333 and continuing applications therefrom, each of U.S. Serial Nos. 13/278,333, 15/063,278, and the above-identified application are owned by Cold Spring Harbor Laboratory.

Cold Spring Harbor Laboratory is also the owner of (assignee of record of the entire right, title and interest in) U.S. Patent No. 9,404,156, issued August 2, 2016, from aforementioned U.S. Serial No. 13/278,333 by virtue of the assignment attached hereto as **Exhibit A**.

IPR2025-01353
Exhibit 1
CSHL EX2001

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 any such 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 any such willful false statement any jeopardize the validity of this application or any patent issued thereon.

Date: 4/27/2023

Cold Spring Harbor Laboratory

By: 

Vladimir Drozdoff, Ph.D., J.D.
Chief Patent Counsel
Office of Technology Transfer
Cold Spring Harbor Laboratory

501787086 01/16/2012

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
James Hicks	11/16/2011
Nicholas Navin	11/14/2011
Jennifer Troge	11/16/2011
Zihua Wang	11/16/2011
Michael Wigler	11/16/2011

RECEIVING PARTY DATA

Name:	Cold Spring Harbor Laboratory
Street Address:	One Bungtown Road
City:	Cold Spring Harbor
State/Country:	NEW YORK
Postal Code:	11724

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	13278333

CH $40.00 13278333

CORRESPONDENCE DATA

Fax Number: (212)391-0525
Phone: 2122780400
Email: patentdocketing@cooperdunham.com
Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent via US Mail.
Correspondent Name: Cooper & Dunham LLP
Address Line 1: 30 Rockefeller Plaza
Address Line 4: New York, NEW YORK 10112

ATTORNEY DOCKET NUMBER:	5981/81503-A/GJG/GC
NAME OF SUBMITTER:	Cindy Shu

Total Attachments: 4
source=120116_5981_81503_A_Assignment_GC_Page_1#page1.tif
source=120116_5981_81503_A_Assignment_GC_Page_2#page1.tif
source=120116_5981_81503_A_Assignment_GC_Page_3#page1.tif
source=120116_5981_81503_A_Assignment_GC_Page_4#page1.tif

Attorney Docket No. 5981/81503-A/GIG/ACK

Assignment of Non-Provisional Application

In consideration of One Dollar ($1.00), and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the undersigned,

James Hicks residing at 3 Great Meadow Road, Locust Valley, NY 11560; Nicholas Navin residing at 1621 Wichita St., Houston, TX 77004; Jennifer Troge residing at 100 Simcoe St., Oyster Bay, NY 11771; Zihua Wang residing at 13 Meadowlawn St., Huntington, NY 11743; and Michael Wigler residing at 52 Snake Hill Road, Cold Spring Harbor, NY 11724

Hereby sell, assign and transfer *to* Cold Spring Harbor Laboratory, *a corporation of the State of* New York, *having a place of business at* One Bungtown Road, Cold Spring Harbor, New York 11724 U.S.A, *in the County of* Suffolk *and State of* New York, *its successors, assigns and legal representatives, the entire right, title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned on* November 16, 2011; November 14, 2011; November 16, 2011; November 16, 2011; and November 16, 2011 *and is entitled*

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

(U.S. Serial No. 13/278,333, filed October 21, 2011, claiming the benefit of U.S. Provisional Application Nos. 61/510,579, filed July 22, 2011 and 61/406,067, filed October 22, 2010)

and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for U.S. Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorize and request *the Commissioner for Patents of the United States to issue to said Assignee, the corporation above named, its successors, assigns and legal representatives, in accordance with this assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;*

JPW Rev. April 19, 2007

Agree *that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives; and*

Covenant *with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.*

Date: 11-16-11

Witness: _____ [signature]

Vladimir Dozoroff [printed name]

102 Cleveland Dr [address]

Centerport, NY 11721

[L.S.]

James Hicks

JPW Rev. April 19, 2007

[L.S.]
Nicholas Navin

Date: 11-14-2011
Witness: _____ [signature]
Jill Waters [printed name]
1515 Holcombe Blvd [address]
Houston TX 77030

[L.S.]
Jennifer Troge

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[L.S.]
Zihua Wang

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[L.S.]
Michael Wigler

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[L.S.]

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[LS]
Nicholas Navin

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[LS]
Jennifer Troge

Date: Nov 8, 2011
Witness: _____ [signature]
Vladimir Drezdzk [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721

[LS]
Zihua Wang

Date: 11/8/2011
Witness: _____ [signature]
Vladimir Drezdzk [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721

[LS]
Michael Wigler

Date: 11/8/2011
Witness: _____ [signature]
Vladimir Drezdzk [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721

[LS]

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1-67. (Cancelled).

68. (Currently Amended) A method comprising:

a) obtaining segments of genomic nucleic acids from a sample;

b) tagging the segments with nucleic acid tags, thereby generating unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;

c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified unique tagged nucleic acid molecules;

d) generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c);

e) assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and

f) obtaining copy number information based on a count of the number of unique tagged nucleic acid molecules that have been assigned to the same location in the genome~~, accounting for sequence error by ignoring unique tagged nucleic acid molecules that differ by a single nucleotide relative to other unique tagged nucleic acid molecules that map to the same location on the genome~~.

69-70. (Cancelled).

71. (Previously Presented) The method of claim 68, wherein the polymerase chain reaction of step c) comprises region specific PCR primers.

72. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules differ at more than one nucleotide or wherein the sequences of the nucleic acid tags are known prior to said generating unique tagged nucleic acid molecules.

73. (Currently Amended) The method of ~~claim 69~~claim 68, wherein the segments of the genomic nucleic acids are produced by mechanical shearing, heating, or sonication of the sample.

74. (Previously Presented) The method of claim 68, wherein the nucleic acid tags comprise a sample tag or a sample tag set.

75. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are double-stranded.

76-81. (Cancelled)

82. (Previously Presented) The method of claim 68, wherein said tagging the segments comprises:

i) adding a polynucleotide tail to the ends of the segments of the genomic nucleic acids, thereby generating zero-th order derivative strands comprising the polynucleotide tail,

ii) subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

iii) subjecting the product of step (ii) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (i) under conditions which promote the formation of only one complement of the product of step (ii), wherein the primers of step (ii) and the primers of step (iii) have different nucleotide sequences, and wherein the polymerase has 3′-5′ proofreading activity,

wherein the primers of at least one of steps (ii) and (iii) comprise nucleic acid tags, such that each of the tagged nucleic acid molecules is unique, thereby generating the unique tagged nucleic acid molecules.

83. (Currently Amended) The method of ~~claim 81~~claim 82, wherein said adding the polynucleotide tail comprises the use of a terminal transferase.

84. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to PCR or the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d).

85. (Previously Presented) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR or prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c).

86. (Previously Presented) The method of claim 85, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads.

87. (Currently Amended) The method of claim 68, wherein the unique tagged nucleic acid molecules ~~tag associated sequence reads~~ are

generated from genomic nucleic acids originating from: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

88. (Previously Presented) The method of claim 68, wherein the sample is a blood sample or bone marrow sample.

89. (New) The method of claim 68, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of genomic nucleic acids.

90. (New) The method of claim 89, wherein the nucleic acid tags are no greater than 1000 nucleotides and no less than two nucleotides long.

91. (New) The method of claim 90, wherein the nucleic acid tags are two to fifteen nucleotides long.

92. (New) The method of claim 90, wherein the nucleic acid tags are six nucleotides long.

93. (New) The method of claim 90, wherein the nucleic acid tags are two nucleotides long.

94. (New) The method of claim 89, wherein the nucleic acid tags vary in length.

95. (New) The method of claim 89, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

96. (New) The method of claim 95, wherein the length of the constant portions and the length of the variable portions is the same.

97. (New) The method of claim 95, wherein the length of the constant portions and the length of the variable portions is different.

98. (New) The method of claim 95, wherein the variable portions consist of only two species of nucleotides.

99. (New) The method of claim 95, wherein the variable portions consist of only three species of nucleotides.

100. (New) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed from a set of dinucleotides.

101. (New) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed from a set of trinucleotides.

102. (New) The method of claim 89, wherein the nucleic acid tags comprise nucleotide sequences that are not known prior to generating tagged nucleic acid molecules.

103. (New) The method of claim 89, wherein the nucleic acid tags comprise random nucleotide sequences.

104. (New) The method of claim 89, wherein the nucleic acid tags are substantially unique nucleic acid tags.

105. (New) The method of claim 68, wherein the nucleic acid tags used to tag the segments of genomic nucleic acids in step b) comprise a sufficiently large number of distinct nucleic acid tags to generate unique tagged nucleic acid molecules.

106. (New) The method of claim 105, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of genomic nucleic acids.

107. (New) The method of claim 106, wherein the nucleic acid tags are no greater than 1000 nucleotides and no less than two nucleotides long.

108. (New) The method of claim 107, wherein the nucleic acid tags are two to fifteen nucleotides long.

109. (New) The method of claim 107, wherein the nucleic acid tags are six nucleotides long.

110. (New) The method of claim 107, wherein the nucleic acid tags are two nucleotides long.

111. (New) The method of claim 105, wherein the nucleic acid tags vary in length.

112. (New) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

113. (New) The method of claim 112, wherein the length of the constant portions and the length of the variable portions is the same.

114. (New) The method of claim 112, wherein the length of the constant portions and the length of the variable portions is different.

115. (New) The method of claim 112, wherein the variable portions consist of only two species of nucleotides.

116. (New) The method of claim 112, wherein the variable portions consist of only three species of nucleotides.

117. (New) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed from a set of dinucleotides.

118. (New) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed from a set of trinucleotides.

119. (New) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences that are not known prior to generating tagged nucleic acid molecules.

120. (New) The method of claim 105, wherein the nucleic acid tags comprise random nucleotide sequences.

121. (New) The method of claim 105, wherein the nucleic acid tags are substantially unique nucleic acid tags.

122. (New) The method of claim 68, wherein the nucleic acid tags are substantially unique nucleic acid tags.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

405 Lexington Avenue
48th Floor
New York, NY 10174
April 27, 2023

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO OCTOBER 27, 2022 OFFICE ACTION

This Amendment is submitted in response to the October 27, 2022 Office Action issued in connection with the above-identified application. A response to the October 27, 2022 Office Action was originally due January 27, 2023. Applicants hereby petition for a three-month extension of time. The fee for a three-month extension of time is five hundred ninety two dollars ($592.00) for a small entity and authorization is hereby given to charge this amount to a credit card linked to Customer Number 1912. With a three-month extension of time, a response is now due April 27, 2023. Accordingly, this Amendment is being timely filed.

Amendments to the Claims begin on page **2** of this paper.
A **Summary of Examiner Interview** begins on page **9** of this paper.
Remarks begin on page **10** of this paper.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR

CONFIRMATION NO. 8088

GARY J. GERSHIK, ESQ.
COOPER & DUNHAM LLP
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

POA ACCEPTANCE LETTER

OC000000057005262

Date Mailed: 05/11/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/25/2023.

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/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
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For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

405 Lexington Avenue
48th Floor
New York, NY 10174
May 15, 2023

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

COMMUNICATION FORWARDING CORRECTED TERMINAL DISCLAIMER

Upon reviewing applicant's April 27, 2023 Amendment and Terminal Disclaimer filing, applicant noted that the Terminal Disclaimer filed on April 27, 2023 is missing a page.

Accordingly, applicant submits herewith, as **Exhibit 1**, a corrected Terminal Disclaimer signed by an authorized official of the assignee of record of U.S. Patent Nos. 9,404,156 and 10,947,589, and of the subject application, namely Cold Spring Harbor Laboratory. This corrected Terminal Disclaimer includes the omitted page.

Under 37 C.F.R. § 1.321(c), a Terminal Disclaimer must be accompanied by the fee set forth in 37 C.F.R. § 1.20(d). Under 37 C.F.R. § 1.20(d), the fee for filing a Terminal Disclaimer is ONE HUNDRED SEVENTY DOLLARS ($170.00). The fee under 37 C.F.R. § 1.20(d) was paid via EFS on April 27, 2023. Accordingly, applicant submits that no further fee is required.

In accordance with pre-AIA 37 C.F.R. § 1.321(b), the Terminal Disclaimer submitted herewith as **Exhibit 1:** (1) is signed by the assignee of record of the entire interest of the subject application, (2) specifies the portion of the term of patent being disclaimed, (3) states the present extent of assignee's ownership interest in the patent to be granted, and (4) is accompanied by the fee set forth in

37 C.F.R. § 1.20(d). Accordingly, the Terminal Disclaimer submitted herewith complies with the requirements of pre-AIA 37 C.F.R. § 1.321(b).

Based on the submission of the Terminal Disclaimer, the double patenting rejection set forth in the October 27, 2022 Office Action has been overcome. Accordingly, applicants respectfully request withdrawal of this rejection.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on May 15, 2023.

/Darren Haber/

Darren Haber

Gary J. Gershik
Registration No. 39,992
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405 Lexington Avenue
48th Floor
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UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
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www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	**05/15/2023 11:53:11 AM ET**	**81503-AAA/GJG/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	62088807	FILING DATE	02/07/2019
CUSTOMER #	–	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	GARY J. GERSHIK, ESQ., COOPER & DUNHAM LLP 30 ROCKEFELLER PLAZA, - NEW YORK, NEW YORK 10112 UNITED STATES	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
230515_81503-AAA_Communication_DH.pdf	2	Supplemental Response or Supplemental Amendment	92 KB
230512_81503-AAA_Communication_Exh1_TerminalDisclaimer_DH.pdf	9	Terminal Disclaimer Filed	928 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)

230515_81503-AAA_Communication_DH.pdf	662DB5B35D8A17BAAAACD36BD675FAB8D14AD89D5DF008C757D8854C752D24DE554DC9A84148D68ECB8345F9D0783A9AE829D9D8DB9C04A2AB0D078C8B2221E4
230512_81503-AAA_Communication_Exh1_TerminalDisclaimer_DH.pdf	4574698216C60A29226F1F0C17F4F33AAC0F256509AFDC6B1B88B2630C39D5E1390AD8416F98384E474C28D28D8675F2EBF86B83392076126ADE55BA51D0265B

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
Inventor(s)	: James Hicks et al.		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
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Cold Spring Barbor Laboratory is also the owner of (assignee of record of the entire right, title and interest in) U.S. Patent No. 9,404,156, issued August 2, 2016, from aforementioned U.S. Serial No. 13/278,333 by virtue of the assignment attached hereto as **Exhibit A**.

IPR2025-01353
Exhibit 1
CSHL EX2001

Cold Spring Harbor Laboratory is also the owner of (assignee of record of the entire right, title and interest in) U.S. Patent No. 10,947,589, issued March 16, 2021, from aforementioned U.S. Serial No. 15/063,278 by virtue of the assignment attached hereto as **Exhibit A**.

Cold Spring Harbor Laboratory hereby disclaims, except as provided below, the terminal part of the term of any patent granted on the above-identified application which would extend beyond the expiration date of the full statutory term of the earliest to expire of U.S. Patent Nos. 9,404,156 and 10,947,589 and hereby agrees that any patent issued from the subject application shall be enforceable only for and during such period that the owner of such patent is the same as the owner of each of U.S. Patent Nos. 9,404,156 and 10,947,589 (i.e. the patents are commonly owned), this agreement to run with any patent granted on the subject application and to be binding upon the grantee, its successors and assigns.

In making the above disclaimer, Cold Spring Harbor Laboratory does not disclaim the terminal part of the term of any patent granted on the subject application that would extend to the expiration date of the full statutory term of such earliest to expire of U.S. Patent Nos. 9,404,156 and 10,947,589 in the event that such earliest to expire patent expires prior to its full statutory term 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 C.F.R. §1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any other manner terminated prior to the expiration date of the full statutory term to which such earliest to expire patent would otherwise have been entitled.

I have reviewed the assignment attached hereto and certify that, to the best of my knowledge and belief, Cold Spring Harbor Laboratory is the assignee of all right, title and interest in and to the subject application and each of U.S. Patent Nos. 9,404,156 and 10,947,589. I further certify that I am authorized to sign this Terminal Disclaimer on behalf of Cold Spring Harbor Laboratory.

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 any such 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 any such willful false statement any jeopardize the validity of this application or any patent issued thereon.

Date: 4/27/2023

Cold Spring Harbor Laboratory

By: _____

Vladimir Drozdoff, Ph.D., J.D.
Chief Patent Counsel
Office of Technology Transfer
Cold Spring Harbor Laboratory

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
James Hicks	11/16/2011
Nicholas Navin	11/14/2011
Jennifer Troge	11/16/2011
Zihua Wang	11/16/2011
Michael Wigler	11/16/2011

RECEIVING PARTY DATA

Name:	Cold Spring Harbor Laboratory
Street Address:	One Bungtown Road
City:	Cold Spring Harbor
State/Country:	NEW YORK
Postal Code:	11724

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	13278333

CH $40.00 13278333

CORRESPONDENCE DATA

Fax Number: (212)391-0525
Phone: 2122780400
Email: patentdocketing@cooperdunham.com
Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent via US Mail.
Correspondent Name: Cooper & Dunham LLP
Address Line 1: 30 Rockefeller Plaza
Address Line 4: New York, NEW YORK 10112

ATTORNEY DOCKET NUMBER:	5981/81503-A/GJG/GC
NAME OF SUBMITTER:	Cindy Shu

Total Attachments: 4
source=120116_5981_81503_A_Assignment_GC_Page_1#page1.tif
source=120116_5981_81503_A_Assignment_GC_Page_2#page1.tif
source=120116_5981_81503_A_Assignment_GC_Page_3#page1.tif
source=120116_5981_81503_A_Assignment_GC_Page_4#page1.tif

Attorney Docket No. 5981/81503-A/GIG/ACK

Assignment of Non-Provisional Application

In consideration of One Dollar ($1.00), and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the undersigned,

James Hicks residing at 3 Great Meadow Road, Locust Valley, NY 11560; Nicholas Navin residing at 1621 Wichita St., Houston, TX 77004; Jennifer Troge residing at 100 Simcoe St., Oyster Bay, NY 11771; Zihua Wang residing at 13 Meadowlawn St., Huntington, NY 11743; and Michael Wigler residing at 52 Snake Hill Road, Cold Spring Harbor, NY 11724

Hereby sell, assign and transfer *to* Cold Spring Harbor Laboratory, *a corporation of the State of* New York, *having a place of business at* One Bungtown Road, Cold Spring Harbor, New York 11724 U.S.A, *in the County of* Suffolk *and State of* New York, *its successors, assigns and legal representatives, the entire right, title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned on* November 16, 2011; November 14, 2011; November 16, 2011; November 16, 2011; and November 16, 2011 *and is entitled*

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

(U.S. Serial No. 13/278,333, filed October 21, 2011, claiming the benefit of U.S. Provisional Application Nos. 61/510,579, filed July 22, 2011 and 61/406,067, filed October 22, 2010)

and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for U.S. Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorize and request *the Commissioner for Patents of the United States to issue to said Assignee, the corporation above named, its successors, assigns and legal representatives, in accordance with this assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;*

JPW Rev. April 19, 2007

Agree *that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives; and*

Covenant *with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.*

Date: 11-16-11

Witness: _____ [signature]

Vladimir Dozoroff [printed name]

102 Cleveland Dr [address]

Centerport, NY 11721

_____ [L.S.]
James Hicks

JPW Rev. April 19, 2007

[L.S.]
Nicholas Navin

Date: 11-14-2011
Witness: _____ [signature]
Jill Waters [printed name]
1515 Holcombe Blvd [address]
Houston TX 77030

[L.S.]
Jennifer Troge

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[L.S.]
Zihua Wang

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[L.S.]
Michael Wigler

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[L.S.]

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[LS]
Nicholas Navin

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

[LS]
Jennifer Troge

Date: Nov 8, 2011
Witness: _____ [signature]
Vladimir Drezdoff [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721

[LS]
Zihua Wang

Date: 11/8/2011
Witness: _____ [signature]
Vladimir Drezdoff [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721

[LS]
Michael Wigler

Date: 11/8/2011
Witness: _____ [signature]
Vladimir Drezdoff [printed name]
107 Cleveland Dr [address]
Centerport, NY 11721

[LS]

Date: _____
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR

CONFIRMATION NO. 8088

GARY J. GERSHIK, ESQ.
COOPER & DUNHAM LLP
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

POA ACCEPTANCE LETTER

OC000000057005262

Date Mailed: 05/11/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/25/2023.

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/

Application Number * 16/269,818 *	Application/Control No. 16/269,818	Applicant(s)/Patent under Reexamination Hicks et al.	
	Examiner LU, FRANK WEI MIN	Art Unit 1634	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 02 June 2023	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

2/Tds both approved.
/LAWANA R HIXON/

Technology Center: OPLC

Telephone: (571)272-6074

_____

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	06/02/2023 10:18:21 AM ET	81503-AAA/GJG/ADR

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	62197203	AUTHORIZED BY	Gary Gershik
CUSTOMER #	--	FILING DATE	02/07/2019
CORRESPONDENCE ADDRESS	GARY J. GERSHIK, ESQ., COOPER & DUNHAM LLP 30 ROCKEFELLER PLAZA, - NEW YORK, NEW YORK 10112 UNITED STATES	FIRST NAMED INVENTOR	James Hicks

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 1044	E202362A19087405	Darren Haber

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	2	340.00
			TOTAL AMOUNT:	$340.00

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 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 [illegible]

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.

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 #
16/269,818	**06/02/2023 10:18:21 AM ET**	**81503-AAA/GJG/ADR**

Title of Invention

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CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	62197203	FILING DATE	02/07/2019
CUSTOMER #	–	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	GARY J. GERSHIK, ESQ., COOPER & DUNHAM LLP 30 ROCKEFELLER PLAZA, - NEW YORK, NEW YORK 10112 UNITED STATES	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
230602_81503-AAA_TerminalDisclaimer1_DH.pdf	2	Terminal Disclaimer Filed	300 KB
230602_81503-AAA_TerminalDisclaimer2_DH.pdf	2	Terminal Disclaimer Filed	303 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
230602_81503-AAA_TerminalDisclaimer1_DH.pdf	2D1F3A0EA4E77B1E62055001C0316A8327A1DD2A3760A8FC3DF300344B98935ABF3AC6E9E378F07EE357304982151041985 7ED0CBF74B139FBBE82720A424746
230602_81503-AAA_TerminalDisclaimer2_DH.pdf	281317D4626E09BE23F3EA16E8815444F68C0E408D74B3C2B44DE015A337ED16BA4E6897E906A2264F205B3A2DF28424936B 2C207521A80DA884E9ABFDE37D4C

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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.

PTO/AIA/26 (04-14)
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 81503-AAA/GJG/DH

In re Application of: Hicks et al.

Application No.: 16/269,818

Filed: February 7. 2019

For: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

The applicant, Cold Spring Harbor Laboratory, owner of 100 percent interest 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 **prior patent** No. 9404156 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** 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 applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

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 presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 39,992

/Gary J. Gershik/ — Signature
June 2, 2023 — Date

Gary J. Gershik — Typed or printed name

Attorney — Title
212-336-8000 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, send to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to: 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law; 2) a Federal, state, local, or international agency, in response to its request; 3) a contractor of the USPTO having need for the information in order to perform a contract; 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record; 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record; 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations; 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals; 8) 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)); 9) the Office of Personnel Management (OPM) for personnel research purposes; and 9) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Additional Uses

Additional USPTO uses of the information in this record may include disclosure to: 1) the International Bureau of the World Intellectual Property Organization, if the record is related to an international application filed under the Patent Cooperation Treaty; 2) the public i) after publication of the application pursuant to 35 U.S.C. 122(b), ii) after issuance of a patent pursuant to 35 U.S.C. 151, iii) 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, or iv) without publication of the application or patent under the specific circumstances provided for by 37 CFR 1.14(a)(1)(v)-(vii); and/or 3) the National Archives and Records Administration, for inspection of records.

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Approved for use through 05/31/2024. OMB 0651-0031
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 81503-AAA/GJG/DH

In re Application of: Hicks et al.

Application No.: 16/269,818

Filed: February 7. 2019

For: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

The applicant, Cold Spring Harbor Laboratory, owner of 100 percent interest 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 **prior patent** No. 10947589 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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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 presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 39,992

/Gary J. Gershik/	June 2, 2023
Signature	Date
Gary J. Gershik	
Typed or printed name	
Attorney	212-336-8000
Title	Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

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A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, send to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

7590 08/10/2023

GARY J. GERSHIK, ESQ.
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NEW YORK, NY 10112

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
08/10/2023	PAPER

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.

Office Action Summary	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	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 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/27/2023.

☐ 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) 68,71-75 and 82-122 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 68,71-75 and 82-122 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 2/7/2019 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

Response to Amendment

1. Applicant's response to the office action filed on April 27, 2023 has been entered. The claims pending in this application are 68, 71-75 and 82-122.

2. In view of newly added claims 89-122, this application contains claims directed to the following patentably distinct species:

(19) the nucleic acid tags are six nucleotides long (claims 92 and 109)

(20) the nucleic acid tags are two nucleotides long (claims 93 and 110)

The species are independent or distinct because these species are directed to different nucleic acid tags which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71-75, 82-91, 94-108, and 111-122.

There is a serious search and/or examination burden for the patentably distinct species as set forth above because the searches for species (19) and (20) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

3. This application further contains claims directed to the following patentably distinct species:

(21) the length of the constant portions and the length of the variable portions is the same (claims 96 and 113)

(22) the length of the constant portions and the length of the variable portions is different (claims 97 and 114)

The species are independent or distinct because these species are directed to different nucleic acid tags which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71-75, 82-95, 98-112, and 115-122.

There is a serious search and/or examination burden for the patentably distinct species as set forth above because the searches for species (21) and (22) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. This application further contains claims directed to the following patentably distinct species:

(23) the variable portions consist of only two species of nucleotides (claims 98 and 115)

(24) the variable portions consist of only three species of nucleotides (claims 99 and 116)

The species are independent or distinct because these species are directed to different nucleic acid tags which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71-75, 82-97, 100-114, and 117-122.

There is a serious search and/or examination burden for the patentably distinct species as set forth above because the searches for species (23) and (24) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

5. This application further contains claims directed to the following patentably distinct species:

(25) the nucleic acid tags comprise variable portions constructed from a set of dinucleotides (claims 100 and 117)

(26) the nucleic acid tags comprise variable portions constructed from a set of trinucleotides (claims 101 and 118)

The species are independent or distinct because these species are directed to different nucleic acid tags which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71-75, 82-99, 102-116, and 119-122.

There is a serious search and/or examination burden for the patentably distinct species as set forth above because the searches for species (25) and (26) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out

supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

A telephone call was made to Mr. Gary Gershik (Reg. No. 39,992) on August 3, 2023 to request an oral election to the above restriction requirement, but did not result in an election being made.

Applicant is reminded that upon the cancelation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

6. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen, Ph.D., can be reached on (571)272-3157.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
August 8, 2023

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

7590 08/16/2023

GARY J. GERSHIK, ESQ.
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30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
08/16/2023	PAPER

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.

Examiner-Initiated Interview Summary	**Application No.** 16/269,818	**Applicant(s)** Hicks et al.		
	Examiner FRANK W LU	**Art Unit** 1634	**AIA (First Inventor to File) Status** No	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
FRANK W LU	Primary Examiner	Telephonic
Mr. Gary Gershik (Reg. No. 39,992)	Attorney of Record	

Date of Interview: 03 August 2023

Issues Discussed:

Election/Restriction

The examiner called Mr.Gershik to ask whether he can select a species from claims 92, 93, 113, and 114, a species from claims 96, 97, 113, and 114, a species from claims 98, 99, 115, and 116, and a species from claims 100, 101, 117, and 118. Mr. Gershik asked the examiner to send a written election of species.

/FRANK W LU/ Primary Examiner, Art Unit 1634	August 3, 2023

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

REMARKS

In this amendment, applicant has amended claim 68 to improve its clarity. Applicant has also cancelled claims 90-91, 93, 107-108, and 110 without prejudice or disclaimer.

Species Election Requirement

I. Nucleic acid tag length

On page 2 of the August 10, 2023 Office Action, the Examiner alleged that the application contains claims directed to the following patentably distinct species:

(1) Nucleic acid tags are six nucleotides long (claims 92 and 109)

(2) Nucleic acid tags are two nucleotides long (claims 93 and 110)

Applicant's response

In response, applicant has cancelled claims 93 and 110. Accordingly, this election of species requirement is now moot. To the extent an election of species is still required, applicant hereby elects nucleic acid tags that are six nucleotides long. All pending claims read on the elected species.

II. Length of the constant and variable portions.

On page 3 of the August 10, 2023 Office Action, the Examiner alleged that the application further contains claims directed to the following patentably distinct species:

(1) The length of the constant portions and the length of the variable portions is the same (claims 96 and 113)

(2) The length of the constant portions and the length of the variable portions is different (claims 97 and 114)

Applicant's response

In response, applicant hereby elects "the length of the constant portions and the length of the variable portions is different". Claims

68, 71, 72-75, 82-89, 92, 94-96, 98-106, 109, 111-113 and 115-122 read on the elected species.

Applicant understands that, as indicated on page 5 of the Office Action, upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim.

III. Variable portions containing two or three species of nucleotides.

On page 5 of the August 10, 2023 Office Action, the Examiner alleged that the application further contains claims directed to the following patentably distinct species:

(1) The variable portions consist of only two species of nucleotides (claims 98 and 115)

(2) The variable portions consist of only three species of nucleotides (claims 99 and 116)

Applicant's response

In response, applicant hereby elects "the variable portions consist of only three species of nucleotides". Claims 68, 71, 72-75, 82-97, 99-114 and 116-122 read on the elected species.

Applicant understands that, as indicated on page 6 of the Office Action, upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim.

IV. Variable portions containing two or three species of nucleotides.

On page 5 of the August 10, 2023 Office Action, the Examiner alleged that the application further contains claims directed to the following patentably distinct species:

(1) The nucleic acid tags comprise variable portions constructed from a set of dinucleotides (claims 100 and 117)

(2) The nucleic acid tags comprise variable portions constructed from a set of trinucleotides (claims 101 and 118)

Applicant's response

In response, applicant hereby elects "the nucleic acid tags comprise variable portions constructed from a set of dinucleotides". Claims 68, 71-75, 82-100, 102-117 and 119-122 read on the elected species.

Applicant understands that, as indicated on page 8 of the Office Action, upon allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

Gary J. Gershik
Registration No. 39,992
Amster Rothstein & Ebenstein LLP
405 Lexington Avenue
48th Floor
New York, NY 10174
(212) 336-8000

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on August 16, 2023.

/Darren Haber/

Darren Haber
Reg. No. 80,964

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
16/269,818	February 7, 2019

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 23432

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☐ The address associated with the above-mentioned Customer Number

OR

☑ The address associated with Customer Number: 23432

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Cold Spring Harbor Laboratory

☐ Inventor or Joint Inventor (title not required below)

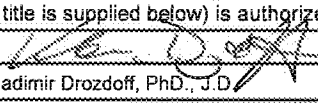
☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	Vladimir Drozdoff, PhD., J.D.		
Title	Chief Patent Counsel		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	**08/16/2023 04:56:50 PM ET**	**81503-AAA/GJ G/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	62628420	FILING DATE	02/07/2019
CUSTOMER #	–	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	GARY J. GERSHIK, ESQ., COOPER & DUNHAM LLP 30 ROCKEFELLER PLAZA, - NEW YORK, NEW YORK 10112 UNITED STATES	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 5

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
230816_81503-AAA_Amendment_DH.pdf		11	-	175 KB
230816_81503-AAA_Amendment_DH-ELC..pdf	(1-1)	1	Response to Election / Restriction Filed	90 KB
230816_81503-AAA_Amendment_DH-CLM.pdf	(2-7)	6	Claims	134 KB
230816_81503-	(8-8)	1	Applicant summary of interview	120 KB

AAA_Amendment_DH-INTRVIEW.APP.pdf			with examiner	
230816_81503-AAA_Amendment_DH-REM.pdf	(9-11)	3	Applicant Arguments/Remarks Made in an Amendment	152 KB
230816_81503-AAA_POA_DH.pdf		1	Power of Attorney	107 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
230816_81503-AAA_Amendment_DH.pdf	28E1F6D23C66E14E4EC4A8533D4700C34225AA084BCC55686 5489AC14C9E9DC5A1AC862DF5C529F93951DC6586E7E49AE 29B439F80935B902A1A4A1F998E1886
230816_81503-AAA_Amendment_DH-ELC..pdf	689BCBC562908D8312D1F5EC5907948EF277094F3213DD7133 41A74A6E9CCB8DDB8F571EF462BB95E05EBD0C8EF2BAD7C A748033D969682BB66E7EA1D38D0B85
230816_81503-AAA_Amendment_DH-CLM.pdf	3F0CF9D67EB5418DDCA091F98EED21712E3B1BF08DCE3C84 F091F9B0EE2E808E04811CCECD9BE4C7D387E27576D265624 10B4B8B89B369C619FE045C9C760C59
230816_81503-AAA_Amendment_DH-INTRVIEW.APP.pdf	F7C032C0F065C6B40AA173E6622C1BDF0D0CAED27702DE58 A7A098FF8D587E70A098A8F1FB42E1BF0BE675D0C910BA1C1 F0E0AFF89DEEB3CFB7DDFCE6FC4DE27
230816_81503-AAA_Amendment_DH-REM.pdf	A3C8A8D5642E8A3B42ED8798B28ED6ACC141D8565EB2F3F5 28D257752C8E0A13386F1340C26DAAC82A7EDD34A585D8B1A 28662A65A62B10135AE64979AC2C974
230816_81503-AAA_POA_DH.pdf	A5194255000D384AA3DCC59902C1215C3C7CA50B7E929B540 2ADBF0D974752668B4854DF8CABED45012D4EC7E318F444E0 C69E2DCF11F909288B0479544DF986

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.

SUMMARY OF AUGUST 15, 2023 EXAMINER INTERVIEW

On August 15, 2023, an Examiner Interview was conducted between Examiner Frank Lu, Darren Haber of the undersigned's office, and the undersigned, Gary Gershik.

During the interview, possible amendments to the claims were discussed. The undersigned indicated that a response to the August 10, 2023 Office Action would be filed along with an amendment to the claims.

The Examiner stated that he would contact the undersigned if any further issues with the claims remain after the amendment is filed.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

405 Lexington Avenue
48th Floor
New York, NY 10174
August 16, 2023

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO AUGUST 10, 2023 OFFICE ACTION (RESTRICTION REQUIREMENT)

This Amendment is submitted in response to the August 10, 2023 Office Action (Restriction Requirement) issued in connection with the above-identified application. A response to the August 10, 2023 Office Action is due October 10, 2023. Accordingly, this Amendment is being timely filed.

Amendments to the Claims begin on page **2** of this paper.
A **Summary of Examiner Interview** begins on page **8** of this paper.
Remarks begin on page **9** of this paper.

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1-67. (Cancelled).

68. (Currently Amended) A method comprising:

a) obtaining segments of genomic nucleic acids from a sample;

b) tagging the segments with nucleic acid tags, thereby generating unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;

c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified unique tagged nucleic acid molecules;

d) generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c);

e) assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and

f) obtaining copy number information based on a count of the number of unique tagged nucleic acid molecules from the sample that have been assigned to the same location in the genome.

69-70. (Cancelled).

71. (Previously Presented) The method of claim 68, wherein the polymerase chain reaction of step c) comprises region specific PCR primers.

72. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules differ at more than one nucleotide or wherein the sequences of the nucleic acid tags are known prior to said generating unique tagged nucleic acid molecules.

73. (Previously Presented) The method of claim 68, wherein the segments of the genomic nucleic acids are produced by mechanical shearing, heating, or sonication of the sample.

74. (Previously Presented) The method of claim 68, wherein the nucleic acid tags comprise a sample tag or a sample tag set.

75. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are double-stranded.

76-81. (Cancelled)

82. (Previously Presented) The method of claim 68, wherein said tagging the segments comprises:

i) adding a polynucleotide tail to the ends of the segments of the genomic nucleic acids, thereby generating zero-th order derivative strands comprising the polynucleotide tail,

ii) subjecting the zero-th order derivative strands of step (i) to a ligation reaction in the presence of primers capable of hybridizing to the polynucleotide tail of the zero-th order strands added in step (i) under conditions that promote the ligation of a primer to the 5′ ends of the zero-th order derivative strands,

iii) subjecting the product of step (ii) to a polymerase reaction in the presence of primers capable of hybridizing to the polynucleotide tail added in step (i) under conditions which promote the formation of only one complement of

the product of step (ii), wherein the primers of step (ii) and the primers of step (iii) have different nucleotide sequences, and wherein the polymerase has 3'-5' proofreading activity,

wherein the primers of at least one of steps (ii) and (iii) comprise nucleic acid tags, such that each of the tagged nucleic acid molecules is unique, thereby generating the unique tagged nucleic acid molecules.

83. (Previously Presented) The method of claim 82, wherein said adding the polynucleotide tail comprises the use of a terminal transferase.

84. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to PCR or the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d).

85. (Previously Presented) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR or prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c).

86. (Previously Presented) The method of claim 85, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads.

87. (Currently Amended) The method of claim 68, wherein the unique tagged nucleic acid molecules are generated from genomic nucleic acids originating from: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

88. (Previously Presented) The method of claim 68, wherein the sample is a blood sample or bone marrow sample.

89. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of genomic nucleic acids.

90. (Cancelled)

91. (Cancelled)

92. (Previously Presented) The method of claim 90, wherein the nucleic acid tags are six nucleotides long.

93. (Cancelled)

94. (Previously Presented) The method of claim 89, wherein the nucleic acid tags vary in length.

95. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

96. (Previously Presented) The method of claim 95, wherein the length of the constant portions and the length of the variable portions is the same.

97. (Previously Presented) The method of claim 95, wherein the length of the constant portions and the length of the variable portions is different.

98. (Previously Presented) The method of claim 95, wherein the variable portions consist of only two species of nucleotides.

99. (Previously Presented) The method of claim 95, wherein the variable portions consist of only three species of nucleotides.

100. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed from a set of dinucleotides.

101. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed from a set of trinucleotides.

102. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise nucleotide sequences that are not known prior to generating tagged nucleic acid molecules.

103. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise random nucleotide sequences.

104. (Previously Presented) The method of claim 89, wherein the nucleic acid tags are substantially unique nucleic acid tags.

105. (Previously Presented) The method of claim 68, wherein the nucleic acid tags used to tag the segments of genomic nucleic acids in step b) comprise a sufficiently large number of distinct nucleic acid tags to generate unique tagged nucleic acid molecules.

106. (Previously Presented) The method of claim 105, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of genomic nucleic acids.

107. (Cancelled)

108. (Cancelled)

109. (Previously Presented) The method of claim 107, wherein the nucleic acid tags are six nucleotides long.

110. (Cancelled)

111. (Previously Presented) The method of claim 105, wherein the nucleic acid tags vary in length.

112. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

113. (Previously Presented) The method of claim 112, wherein the length of the constant portions and the length of the variable portions is the same.

114. (Previously Presented) The method of claim 112, wherein the length of the constant portions and the length of the variable portions is different.

115. (Previously Presented) The method of claim 112, wherein the variable portions consist of only two species of nucleotides.

116. (Previously Presented) The method of claim 112, wherein the variable portions consist of only three species of nucleotides.

117. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed from a set of dinucleotides.

118. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed from a set of trinucleotides.

119. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences that are not known prior to generating tagged nucleic acid molecules.

120. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise random nucleotide sequences.

121. (Previously Presented) The method of claim 105, wherein the nucleic acid tags are substantially unique nucleic acid tags.

122. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are substantially unique nucleic acid tags.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR

CONFIRMATION NO. 8088

GARY J. GERSHIK, ESQ.
COOPER & DUNHAM LLP
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

POWER OF ATTORNEY NOTICE

OC000000060792885

Date Mailed: 08/22/2023

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/16/2023.

- The Power of Attorney to you in this application has been revoked by the applicant. 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/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR

CONFIRMATION NO. 8088

23432
Gary J. Gershik; John P. White;
Christopher C. Dunham; Paul Teng
405 LEXINGTON AVENUE
NEW YORK, NY 10174

POA ACCEPTANCE LETTER

OC000000060793035

Date Mailed: 08/22/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/16/2023.

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/

IFW

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

7590 08/10/2023

GARY J. GERSHIK, ESQ.
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30 ROCKEFELLER PLAZA
NEW YORK, NY 10112



EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
08/10/2023	PAPER

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.

PTOL-90A (Rev. 04/07)

IPR2025-01353
CSHL EX2001

OPAP LHDTSV-4
AUG 2 9 2023
PATENT & TRADEMARK OFFICE

Office Action Summary	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	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 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/27/2023.

☐ 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) 68,71-75 and 82-122 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 68,71-75 and 82-122 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 2/7/2019 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: _____.

OPAP LHDTSV-4
AUG 2 9 2023
PATENT & TRADEMARK OFFICE

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on April 27, 2023 has been entered. The claims pending in this application are 68, 71-75 and 82-122.

2. In view of newly added claims 89-122, this application contains claims directed to the following patentably distinct species:

(19) the nucleic acid tags are six nucleotides long (claims 92 and 109)

(20) the nucleic acid tags are two nucleotides long (claims 93 and 110)

The species are independent or distinct because these species are directed to different nucleic acid tags which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71-75, 82-91, 94-108, and 111-122.

There is a serious search and/or examination burden for the patentably distinct species as set forth above because the searches for species (19) and (20) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

IPR2025-01353
CSHL EX2001

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

3. This application further contains claims directed to the following patentably distinct species:

(21) the length of the constant portions and the length of the variable portions is the same (claims 96 and 113)

(22) the length of the constant portions and the length of the variable portions is different (claims 97 and 114)

The species are independent or distinct because these species are directed to different nucleic acid tags which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71-75, 82-95, 98-112, and 115-122.

There is a serious search and/or examination burden for the patentably distinct species as set forth above because the searches for species (21) and (22) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

IPR2025-01353
CSHL EX2001

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. This application further contains claims directed to the following patentably distinct species:

(23) the variable portions consist of only two species of nucleotides (claims 98 and 115)

(24) the variable portions consist of only three species of nucleotides (claims 99 and 116)

The species are independent or distinct because these species are directed to different nucleic acid tags which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71-75, 82-97, 100-114, and 117-122.

There is a serious search and/or examination burden for the patentably distinct species as set forth above because the searches for species (23) and (24) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

5. This application further contains claims directed to the following patentably distinct species:

(25) the nucleic acid tags comprise variable portions constructed from a set of dinucleotides (claims 100 and 117)

(26) the nucleic acid tags comprise variable portions constructed from a set of trinucleotides (claims 101 and 118)

The species are independent or distinct because these species are directed to different nucleic acid tags which have different properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, generic claims are claims 68, 71-75, 82-99, 102-116, and 119-122.

There is a serious search and/or examination burden for the patentably distinct species as set forth above because the searches for species (25) and (26) are not overlap.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out

supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

A telephone call was made to Mr. Gary Gershik (Reg. No. 39,992) on August 3, 2023 to request an oral election to the above restriction requirement, but did not result in an election being made.

Applicant is reminded that upon the cancelation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

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6. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen, Ph.D., can be reached on (571)272-3157.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
August 8, 2023

EFW

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

7590 08/16/2023

GARY J. GERSHIK, ESQ.
COOPER & DUNHAM LLP
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112



EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
08/16/2023	PAPER

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.

Examiner-Initiated Interview Summary	Application No. 16/269,818	Applicant(s) Hicks et al.		
	Examiner FRANK W LU	Art Unit 1634	AIA (First Inventor to File) Status No	Page 1 of 1

OPAP LADTSV-4
AUG 2 9 2023
PATENT & TRADEMARK OFFICE

All Participants (applicant, applicants representative, PTO personnel)	Title	Type
FRANK W LU	Primary Examiner	Telephonic
Mr. Gary Gershik (Reg. No. 39,992)	Attorney of Record	

Date of Interview: 03 August 2023

Issues Discussed:

Election/Restriction

The examiner called Mr.Gershik to ask whether he can select a species from claims 92, 93, 113, and 114, a species from claims 96, 97, 113, and 114, a species from claims 98, 99, 115, and 116, and a species from claims 100, 101, 117, and 118. Mr. Gershik asked the examiner to send a written election of species.

/FRANK W LU/ Primary Examiner, Art Unit 1634	August 3, 2023

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Organization _____ Bldg/Room _____

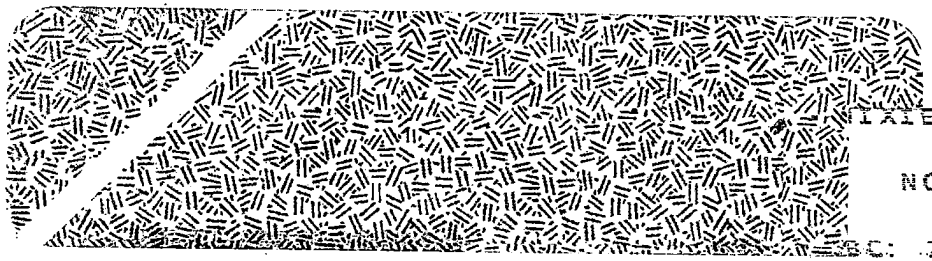
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR

CONFIRMATION NO. 8088

GARY J. GERSHIK, ESQ.
COOPER & DUNHAM LLP
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

POWER OF ATTORNEY NOTICE

OC000000060792885

Date Mailed: 08/22/2023

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 08/16/2023.

- The Power of Attorney to you in this application has been revoked by the applicant. 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/

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L3096	568	(tag OR adaptor OR adapter OR linker) SAME (amplif$ OR PCR) SAME sequence NEAR read SAME genome SAME copy NEAR number	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/11/03 02:40 PM
L3097	335	(tag OR adaptor OR adapter OR linker) SAME (amplif$ OR PCR) SAME sequence NEAR read SAME map$ SAME genome SAME copy NEAR number	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/11/03 02:40 PM
L3098	237	(tag OR adaptor OR adapter OR linker) SAME (amplif$ OR PCR) SAME sequence NEAR read SAME map$ SAME genome SAME count$ SAME copy NEAR number	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/11/03 02:41 PM
L3099	42	(tag OR adaptor OR adapter OR linker) SAME (amplif$ OR PCR) SAME sequence	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU,	OR	ON	ON	2023/11/03 02:41 PM

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GSHL EX2001

		NEAR read SAME map$ SAME genome SAME count$ near10 copy NEAR number	CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L3100	41	L3099 AND ((Y02A90/10 OR G06F17/10 OR G06F17/11 OR G16H10/40 OR G16H50/20 OR G16H50/70 OR C12N15/1093 OR C12N15/1065 OR C12N15/1068 OR C12N15/1096 OR G16B25/00 OR G16B30/00 OR G16B20/10 OR G16B20/00 OR G16B20/20 OR G16B5/00 OR G16B30/10 OR G16B40/00 OR G16B5/20 OR G16B25/20 OR G16B10/00 OR G16B20/40 OR G16B15/00 OR G16B25/10 OR G16B30/20 OR C12Q1/6869 OR C12Q1/6874 OR C12Q1/6886 OR C12Q2600/156 OR C12Q1/683 OR C12Q1/6881 OR C12Q2525/191 OR C12Q2535/122 OR C12Q2563/179 OR C12Q2525/155 OR C12Q2537/159 OR C12Q2537/16 OR C12Q1/686 OR C12Q1/6827 OR C12Q1/6806 OR C12Q1/6855 OR C12Q1/6883 OR C12Q1/6888 OR C12Q1/689 OR	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2023/11/03 02:43 PM

IPR2025-01353
GSHL EX2001

		C12Q2600/16 OR C12Q2600/166 OR C12Q1/68 OR C12Q1/6809 OR C12Q1/6844 OR C12Q2521/107 OR C12Q2537/143 OR C12Q2537/165 OR C12Q2600/158).cpc.)					

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	Art Unit
	FRANK W LU	1634

CPC - Searched*		
Symbol	Date	Examiner
Update	11/03/2023	/FL/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
Update	11/03/2023	/FL/

US Classification - Searched*			
Class	Subclass	Date	Examiner
Update		11/03/2023	/FL/

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Update (see attached file)	11/03/2023	/FL/

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

/FRANK W LU/ Primary Examiner, Art Unit 1634	November 3, 2023

IPR2025-01353
GSK-1202001

Notice of References Cited	Application/Control No. 16/269,818	Applicant(s)/Patent Under Reexamination Hicks et al.	
	Examiner FRANK W LU	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-8715967-B2	05-2014	Casbon; James	G16B20/10	435/6.12
*	B	US-20070031857-A1	02-2007	Makarov; Vladimir L.	C12N15/1068	435/6.1
*	C	US-20050214812-A1	09-2005	Li, Zheng	C12Q1/6827	435/6.12
	D					
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	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	Xie et al., CNV-seq, a new method to detect copy number variation using high-throughput sequencing. BMC Bioinformatics, 10, 80, March 6, 2009.
	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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 11/09/2023

Gary J. Gershik; John P. White
405 LEXINGTON AVENUE
NEW YORK, NY 10174

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/09/2023	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):

PTODOCKET@ARELAW.COM
klees@ARELAW.com
patcomm-in-grp@cooperdunham.com

Office Action Summary	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	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 8/16/2023.

☐ 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) 68,71-75,82-89,92,94-106,109 and 111-122 is/are pending in the application.

5a) Of the above claim(s) 96,98,101,113,115 and 118 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68,71-75,82-89,92,94-95,97,99-100,102-106,109,111-112,114,116-117 and 119-122 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 2/7/2019 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

Election/Restrictions

1. Applicant's election of species (22) (the length of the constant portions and the length of the variable portions is different, see claims 97 and 114), species (24) (the variable portions consist of only three species of nucleotides, see claims 99 and 116), and species (25) (the nucleic acid tags comprise variable portions constructed from a set of dinucleotides, see claims 100 and 117) in the reply filed on August 16, 2023 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.01(a)). Claims 68, 71-75, 82-89, 92, 94, 95, 97, 99, 100, 102-106, 109, 111, 112, 114, 116, 117, and 119-122 will be examined.

Claim Objections

2. Claim 68 is objected to because of the following informalities: (1) "segments of genomic nucleic acids from a sample" in step a) should be "segments of the genomic nucleic acids from a sample containing genomic nucleic acids"; and (2) "from the sample" in step f) should be "in the genomic nucleic acids from the sample".

3. Claim 71 is objected to because of the following informality: "wherein the polymerase chain reaction of step c) comprises region specific PCR primers" should be "wherein the polymerase chain reaction is performed in the presence of region specific PCR primers".

4. Claim 73 is objected to because of the following informality: "mechanical shearing, heating, or sonication of the sample" should be "mechanical shearing, heating, or sonicating the genomic nucleic acids from the sample".

5. Claim 82 is objected to because of the following informalities: (1) "said tagging the segments" in lines 1 and 2 should be "said tagging the segments with nucleic acid tags"; and (2) "nucleic acid tags" in the "wherein" phrase of the end of the claim should be "the nucleic acid tags".

6. Claim 83 is objected to because of the following informality: "said adding the polynucleotide tail comprises the use of a terminal transferase" should be "said adding the polynucleotide tail to the ends of the segments of the genomic nucleic acids is performed in the presence of a terminal transferase".

7. Claim 84 is objected to because of the following informality: "PCR" should be "the PCR".

8. Claim 87 is objected to because of the following informality: "the unique tagged nucleic acid molecules are generated from genomic nucleic acids originating from: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes" should be "the genomic nucleic acids are from a single species, a single cell, two or more organisms, two or more species, or from a population of microbes".

9. Claim 89 or 106 is objected to because of the following informality: "the segments of genomic nucleic acids" should be "the segments of the genomic nucleic acids".

10. Claim 97 or 114 is objected to because of the following informality: "is different" should be 'are different".

11. Claim 102 or 119 is objected to because of the following informality: "generating tagged nucleic acid molecules" should be "said generating tagged nucleic acid molecules".

12. Claim 105 is objected to because of the following informality: "the nucleic acid tags used to tag the segments of genomic nucleic acids in step b) comprise a sufficiently large number of

distinct nucleic acid tags to generate unique tagged nucleic acid molecules" should be "the nucleic acid tags comprise a sufficiently large number of distinct nucleic acid tags".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. 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.

14. Claims 68, 71-75, 82-89, 92, 94, 95, 97, 99, 100, 102-106, 109, 111, 112, 114, 116, 117, and 119-122 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.

15. Claim 68 is rejected as vague and indefinite in view of step f) because it is unclear that copy number information is copy number information of which nucleic acid. Please clarify.

16. Claim 92 recites the limitation "claim 90" in the claim. There is insufficient antecedent basis for this limitation in the claim since claim 90 has been deleted. Please clarify.

17. Claim 109 recites the limitation "claim 107" in the claim. There is insufficient antecedent basis for this limitation in the claim since claim 107 has been deleted. Please clarify.

Claim Rejections - 35 USC § 103

18. 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 negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

19. Claims 68, 71, 72, 74, 75, 84, 87-89, 94, 95, 103-106, 111, 112, and 120-122 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Casbon *et al., (*US 8, 715,967 B2, priority date: September 21, 2010) in view of Xie *et al.,* (BMC Bioinformatics, 10, 80, March 6, 2009).

Regarding claims 68, 71, 72, 74, 75, 84, 87-89, 95, 103-106, 112, and 120-122, Casbon *et al.,* teach a) obtaining segments of genomic nucleic acids from a sample; b) tagging the segments with nucleic acid tags (ie., a set of adaptors), thereby generating unique tagged nucleic acid molecules, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags; c) subjecting the unique tagged nucleic acid molecules (ie., a population of initial target

nucleic acid molecules) to a polymerase chain reaction (PCR), thereby generating amplified unique tagged nucleic acid molecules; and d) generating tag associated sequence reads (ie., a plurality of sequence reads) by sequencing the amplified unique tagged nucleic acid molecules of step (c) as recited in claim 68 wherein the polymerase chain reaction of step c) comprises region specific PCR primers (ie., a sequence specific primer) as recited in claim 71, the sequences of the nucleic acid tags (ie., a set of adaptors) are known prior to said generating unique tagged nucleic acid molecules as recited in claim 72, the nucleic acid tags comprise a sample tag or a sample tag set as recited in claim 74, the nucleic acid tags are double-stranded as recited in claim 75, the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d) as recited in claim 84, the unique tagged nucleic acid molecules are generated from genomic nucleic acids originating from: a single species, a single cell, two or more organisms, two or more species, or from a population of microbes as recited in claim 87, the sample is a blood sample as recited in claim 88, the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of the genomic nucleic acids as recited in claims 89 and 106, the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions as recited in claims 95 and 112, the nucleic acid tags comprise random nucleotide sequences as recited in claims 103 and 120, the nucleic acid tags are substantially unique nucleic acid tags as recited in claim 104, 121, and 122, the nucleic acid tags used to tag the segments of genomic nucleic acids in step b) comprise a sufficiently large number of distinct nucleic acid tags to generate unique tagged nucleic acid molecules as recited in claim 105 (see column 2, second paragraph, column 11, third paragraph, columns 13 and 14, column 24, third and fourth paragraphs, and claims 1-22).

Regarding claims 94 and 111, since Casbon *et al.,* teach that reflex sequences have a wide range of lengths and sequences and are added to adaptors (see column 10, second paragraph), Casbon *et al.,* disclose that the nucleic acid tags vary in length.

Casbon *et al.,* do not disclose e) assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and f) obtaining copy number information based on a count of the number of unique tagged nucleic acid molecules from the sample that have been assigned to the same location in the genome as recited in claim 68. However, Casbon *et al.,* teach estimating, using a computer, the number of initial target nucleic acid molecules that comprise said target region in said tagged sample based on: (i) a determination of the number of said different DBR sequences that are associated with said target region in the sequence reads; and (ii) a determination of the number of sequence reads that comprise each of the different DBR sequences that are associated with said target region (see claim 1).

Xie *et al.,* teach to map two sets of shotgun reads by sequence alignment on a template genome wherein the mapped region is analyzed using a sliding window approach and DNA copy number variations (CNVs) are detected by computing the number of reads for each individual in each of the windows, yielding ratio (see page 2, left column, last paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 68 by assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome and obtaining copy number information based on a count of the number of unique tagged nucleic acid molecules from the sample that have been assigned to the same location in the genome in

view of the prior arts of Casbon *et al.,* and Xie *et al.*. One having ordinary skill in the art would have been motivated to do so because Casbon *et al.,* have successfully estimated, using a computer, the number of initial target nucleic acid molecules that comprise said target region in said tagged sample based on: (i) a determination of the number of said different DBR sequences that are associated with said target region in the sequence reads; and (ii) a determination of the number of sequence reads that comprise each of the different DBR sequences that are associated with said target region (see claim 1) while Xie *et al.,* teach to map two sets of shotgun reads by sequence alignment on a template genome wherein the mapped region is analyzed using a sliding window approach and DNA copy number variations (CNVs) are detected by computing the number of reads for each individual in each of the windows, yielding ratio (see page 2, left column, last paragraph). One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to map each of the plurality of sequence reads taught by Casbon *et al.,* to a location in a genome in view of the prior arts of Casbon *et al.,* and Xie *et al.*, in order to assign each of the amplified unique tagged nucleic acid molecules to a location on a genome and obtain copy number information of a population of initial nucleic acid molecules based on a count of the number of the amplified unique tagged nucleic acid molecules that have been assigned to the same location in the genome.

20. Claim 73 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Casbon *et al.,* in view of Xie *et al.,* as applied to claims 68, 71, 72, 74, 75, 84, 87-89, 94, 95, 103-106, 111, 112, and 120-122 above, and further in view of Makarov *et al.,* (US 2007/0031857 A1, published on February 8, 2007).

The teachings of Casbon *et al.,* and Xie *et al.,* have been summarized previously, *supra.*

Casbon *et al.,* and Xie *et al.,* do not disclose that the segments of the genomic nucleic acids are produced by mechanical shearing, heating, or sonication of the sample as recited in claim 73.

Makarov *et al.,* teach ligation of double stranded adaptors to DNA fragments produced by sonication, nebulization or hydro-shearing (see paragraph [0008]).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 73 wherein the segments of the genomic nucleic acids are produced by mechanical shearing, heating, or sonication of the sample in view of the prior arts of Casbon *et al.,* Xie *et al.,* and Makarov *et al.*. One having ordinary skill in the art would have been motivated to do so because Makarov *et al.,* have successfully ligated double stranded adaptors to DNA fragments produced by sonication, nebulization or hydro-shearing (see paragraph [0008]) and the simple substitution of one kind of the segments of genomic nucleic acids (ie., the segments of genomic nucleic acids taught by Casbon *et al.,*) from another kind of the segments of genomic nucleic acids (ie., the DNA fragments produced by sonication, nebulization or hydro-shearing taught by Makarov *et al.,*) during the process of performing the method recited in claim 68, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the segments of genomic nucleic acids taught by Casbon *et al.,* and DNA fragments produced by sonication, nebulization or hydro-shearing taught by Makarov *et al.,* are used for the same purpose and are exchangeable. One having ordinary skill in the art at the time the invention was made would have a reasonable expectation of success to perform the method recited in claim 73 using the DNA fragments produced by

sonication, nebulization or hydro-shearing taught by Makarov *et al.,* in view of the prior arts of Casbon *et al.,* Xie *et al.,* and Makarov *et al.*.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

21. Claims 92 and 107 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Casbon *et al.,* in view of Xie *et al.,* as applied to claims 68, 71, 72, 74, 75, 84, 87-89, 94, 95, 103-106, 111, 112, and 120-122 above, and further in view of Li *et al.,* (US 2005/0214812 A1, published on September 29, 2005).

The teachings of Casbon *et al.,* and Xie *et al.,* have been summarized previously, *supra.*

Casbon *et al.,* and Xie *et al.,* do not disclose that the nucleic acid tags are six nucleotides long as recited in claims 92 and 107.

Li *et al.,* teach that "[A] given sequencing platform adapter of interest may vary in length, and in some instances may range from 4 to 200 nucleotides in length. For example, the adapter may be from 4 to 100 nucleotides in length, such as from 6 to 75, from 8 to 50, or from 10 to 40 nucleotides in length" (see paragraph [0158]).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the methods recited in claims 92 and 107

using nucleic acid tags having a length of six nucleotides in view of the prior arts of Casbon *et al.,* Xie *et al.,* and Li *et al.*. One having ordinary skill in the art would have been motivated to do so because Li *et al.,* teach that the nucleic acid adapters can be 4 to 100 nucleotides in length (see paragraph [0158]) and optimization of lengths of the nucleic acid adapters during the process for performing the method recited in claim 68, in the absence of convincing evidence to the contrary, would have been obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform the methods recited in claims 92 and 107 using nucleic acid tags having a length of six nucleotides in view of the prior arts of Casbon *et al.,* Xie *et al.,* and Li *et al.*. More particularly, where 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. Where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Response to Arguments

22. Applicant's arguments with respect to claims 68, 70-75, and 82-88 have been considered but are moot because the new ground of rejection does not rely on any reference applied in the prior rejection of record for any teaching or matter specifically challenged in the argument.

Conclusion

23. 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.

24. No claim is allowed.

25. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen, Ph.D., can be reached on (571)272-3157.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
November 3, 2023

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 04/01/2024

Gary J. Gershik; John P. White
405 LEXINGTON AVENUE
NEW YORK, NY 10174

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
04/01/2024	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.

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patcomm-in-grp@cooperdunham.com

Applicant-Initiated Interview Summary	**Application No.** 16/269,818	**Applicant(s)** Hicks et al.		
	Examiner FRANK W LU	**Art Unit** 1634	**AIA (First Inventor to File) Status** No	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
FRANK W LU	Primary Examiner	Telephonic
Mr.Gary Gershik (Reg. No. 39,992)	Attorney of Record	
Mr.Darren Haber		

Date of Interview: 27 March 2024

Issues Discussed:

Proposed Amendment(s)

Applicant's representatives and the examiner discussed the rejections and possible amendments. Applicant will file a response.

/FRANK W LU/ Primary Examiner, Art Unit 1634	March 27, 2024

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	**04/01/2024 01:35:54 PM Z ET**	**81503-AAA/GJG/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	64915280	FILING DATE	02/07/2019
CUSTOMER #	23432	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
240401_81503-AAA_Auth_DH.pdf	2	Internet Communications Authorization	213 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
240401_81503-AAA_Auth_DH.pdf	8F25077D37DA68F06B9406EE8C05E9A3500505D97EC0C27A813F7B8C0E0A02A74B3B7B0B057E913183168597CCAE066926570FA61415A6FB386B6833FBDC7E4F

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: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorization/Internet Communications Authorization Withdrawal

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	16/269,818
	Filing Date	February 7, 2019
	First Named Inventor	James Hicks
	Art Unit	1634
	Examiner Name	Frank Lu
	Practitioner Docket No.	81503-AAA/GJG/DH

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

I. To authorize permission for Internet Communications.

☒ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 39,992.

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

/Gary J. Gershik/ — Signature

April 1, 2024 — Date

Gary J. Gershik — Typed or printed name

212-336-8000 — 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. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

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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 disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 04/12/2024

Gary J. Gershik; John P. White
405 LEXINGTON AVENUE
NEW YORK, NY 10174

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
04/12/2024	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):

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klees@ARELAW.com
patcomm-in-grp@cooperdunham.com

Applicant-Initiated Interview Summary	**Application No.** 16/269,818	**Applicant(s)** Hicks et al.		
	Examiner FRANK W LU	**Art Unit** 1634	**AIA (First Inventor to File) Status** No	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
FRANK W LU	Primary Examiner	Telephonic
Mr. Gary Gershik (Reg. No. 39,992)	Attorney of Record	

Date of Interview: 08 April 2024

Issues Discussed:

Proposed Amendment(s)

Mr. Gershik and the examiner discussed the rejections and possible amendment. The examiner suggested to have another interview which includes the inventors.

/FRANK W LU/ Primary Examiner, Art Unit 1634	April 8, 2024

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/269,818	Filing Date 02/07/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	05/09/2024	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 36	Minus	** 47	= 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

		(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 $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".	/YOLANDA CHADWICK/
*** 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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REMARKS

In this amendment, applicant has amended claim 68 to improve its clarity and to recite "randomly" tagging in step (b), support for which may be found in the subject specification as filed, *inter alia*, at page 46, line 26. Applicant has also amended claims 71, 73, 84, 87, 89, 92, 97, 106, 109, 114 to improve the wording of these claims in accordance with the Examiner's requests in the November 9, 2023 Office Action. Finally, applicant has cancelled claims 82-83 and 102-104 to expedite prosecution.

Claim Objections

In the November 9, 2023 Office Action, the Examiner objected to claims 68, 71, 73, 82, 83, 87, 89, 97, 102, 105, 106, 114, and 119.

Applicant's response

In response, applicant has amended claims 68, 71, 73, 82, 83, 87, 89, 97, 102, 105, 106, 114, and 119 in an effort to overcome the Examiner's objections. Applicant has also cancelled claims 82-83 and 102 to expedite prosecution.

Claim Rejections – 35 U.S.C. § 112 (indefiniteness)

On page 4 of the November 9, 2023 Office Action, the Examiner rejected claims 68, 71-75, 82-89, 92, 94, 95, 97, 99, 100, 102-106, 111, 112, 114, 116, 117, and 119-122 under 35 U.S.C. § 112 (pre-AIA), second paragraph, as allegedly indefinite. The Examiner alleged that claim 68 is vague and indefinite in view of step f) "because it is unclear that copy number information is copy number information of which nucleic acid". The Examiner also alleged that claims 92 and 109 are indefinite because they depend from claims that have been cancelled.

Applicant's response

In response, applicant has amended claim 68 to clarify that the copy number information is "of the genomic nucleic acids from the sample".

Further, applicant has amended claim 92 to depend from pending claim 89, and amended claim 109 to depend from pending claim 106.

Claim Rejections – 35 U.S.C. § 103 (obviousness)

In the November 9, 2023 Office Action, the Examiner rejected claims 68, 71, 72, 74, 75, 84, 87-89, 94, 95, 103-106, 111, 112, and 120-122 under pre-AIA § 103(a) as allegedly unpatentable over Casbon et al. (U.S. Patent No. 8,715,967 B2) in view of Xie et al. The Examiner also rejected claim 73 as allegedly unpatentable over Casbon et al. in view of Xie et al. in further view of Makarov et al. (U.S. Patent Application Publication No. US 2007/0031857 A1) and rejected claims 97 and 107 as allegedly unpatentable over Casbon et al. in view of Xie et al. in further view of Li et al. (US Patent Application Publication No. 2005/0214812 A1). The Examiner's reasons for these rejections are provided on pages 4-11 of the November 9, 2023 Office Action and are addressed below.

Applicant's response

In response, as discussed during the May 7, 2024 Examiner Interview summarized above, the claimed method improves upon the methods described in the cited art, *inter alia*, by (1) randomly tagging segments of genomic nucleic acids to generate the unique tagged nucleic acid molecules, (2) assigning each amplified unique tagged nucleic acid molecule to a location on the genome by mapping each tag associated sequence read to a location on the genome, and (3) obtaining copy number information based on a count of the number of unique tagged nucleic acid molecules that have been assigned to the same location in the genome, rather than based on the number of different tags.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the fee of five hundred ninety two dollars ($592.00) for a small entity for a three-month extension of time and the fee of eight hundred dollars ($800.00) for a small entity a second or subsequent Request for Continued Examination (RCE), is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

_____

Gary J. Gershik
Registration No. 39,992
Amster Rothstein & Ebenstein LLP
405 Lexington Avenue
48th Floor
New York, NY 10174
(212) 336-8000

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on May 9, 2024.

/Darren Haber/

_____
Darren Haber
Reg. No. 80,964

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. 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	16/269,818	Filing Date	2019-02-17	Docket Number (if applicable)	81503-AAA/GJG/DH	Art Unit	2634
First Named Inventor	James Hicks			Examiner Name	Frank Lu		

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

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. 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	/Gary J. Gershik/	Date (YYYY-MM-DD)	2024-05-09
Name	Gary J. Gershik	Registration Number	39992

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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	05/09/2024 04:46:39 PM Z ET	81503-AAA/GJG/ADR

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	65448440	AUTHORIZED BY	Gary Gershik
CUSTOMER #	23432	FILING DATE	02/07/2019
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	James Hicks

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 1036	E202459G48015604	Darren Haber

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2253	EXTENSION FOR RESPONSE WITHIN THIRD MONTH -	592.00	1	592.00
2820	REQUEST FOR CONTINUED EXAMINATION (RCE)- 2ND AND SUBSEQUENT REQUEST (SEE 37 CFR 1.114)	800.00	1	800.00
			TOTAL AMOUNT:	$1,392.00

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 described in MPEP 503.

IPR2025-01353
CSHL EX2001

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.

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Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	**05/09/2024 04:46:39 PM Z ET**	**81503-AAA/GJG/ADR**

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CUSTOMER #	23432	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 5

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
240509_81503-AAA_Amendment_DH.pdf		11	-	183 KB
240509_81503-AAA_Amendment_DH-AMSB.pdf	(1-1)	1	Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)	94 KB
240509_81503-AAA_Amendment_DH-CLM.pdf	(2-7)	6	Claims	138 KB
240509_81503-	(8-8)	1	Applicant summary of interview	123 KB

IPR2025-01353
CSHL EX2001

AAA_Amendment_DH-INTRVIEW.APP.pdf			with examiner	
240509_81503-AAA_Amendment_DH-REM.pdf	(9-11)	3	Applicant Arguments/Remarks Made in an Amendment	156 KB
240509_81503-AAA_RCE_DH.pdf		3	Request for Continued Examination (RCE)	786 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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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.

SUMMARY OF MARCH 27, 2024 EXAMINER INTERVIEW

On March 27, 2024, an Examiner Interview was conducted between Examiner Frank Lu, Darren Haber of the undersigned's office, and the undersigned, Gary Gershik.

During the interview, Applicant's representatives and the Examiner discussed the outstanding rejections and possible amendments to the claims.

SUMMARY OF APRIL 8, 2024 EXAMINER INTERVIEW

On April 8, 2024, an Examiner Interview was conducted between Examiner Frank Lu and the undersigned, Gary Gershik.

During the interview, the undersigned and the Examiner discussed the outstanding rejections and possible amendments to the claims. The Examiner suggested that a further interview be conducted.

SUMMARY OF MAY 7, 2024 EXAMINER INTERVIEW

On May 7, 2024, an Examiner Interview was conducted between Examiner Frank Lu, Dr. Vladimir Drozdoff as a representative of the Applicant, Darren Haber of the undersigned's office, and the undersigned, Gary Gershik.

During the interview, an explanation of the claimed method was provided to the Examiner. It was agreed that claim 68 would be amended to recite "randomly tagging" in step b) to further distinguish the claims from the cited art.

The Examiner stated that he would contact the undersigned if any further issues with the claims remain after the amendment is filed.

Applicant thanks the Examiner for the courtesy extended during each of the interviews summarized above.

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1-67. (Cancelled).

68. (Currently Amended) A method comprising:

a) obtaining segments of genomic nucleic acids from a sample containing the genomic nucleic acids;

b) randomly tagging the segments with nucleic acid tags, thereby generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;

c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified unique tagged nucleic acid molecules;

d) generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c);

e) assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and

f) obtaining copy number information of the genomic nucleic acids from the sample based on a count of the number of unique tagged nucleic acid molecules ~~from the sample~~ that have been assigned to the same location in the genome.

69-70. (Cancelled).

71. (Currently Amended) The method of claim 68, wherein the polymerase chain reaction ~~of step c) comprises~~ is performed in the presence of region specific PCR primers.

72. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules differ at more than one nucleotide or wherein the sequences of the nucleic acid tags are known prior to said generating unique tagged nucleic acid molecules.

73. (Currently Amended) The method of claim 68, wherein the segments of the genomic nucleic acids are produced by mechanical shearing, heating, or ~~sonication of~~ sonicating the genomic nucleic acids from the sample.

74. (Previously Presented) The method of claim 68, wherein the nucleic acid tags comprise a sample tag or a sample tag set.

75. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are double-stranded.

76-83. (Cancelled)

84. (Currently Amended) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to the PCR or the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d).

85. (Previously Presented) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR or prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c).

86. (Previously Presented) The method of claim 85, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads.

87. (Currently Amended) The method of claim 68, wherein the ~~unique tagged nucleic acid molecules are generated from~~ genomic nucleic acids are from ~~originating from:~~ a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

88. (Previously Presented) The method of claim 68, wherein the sample is a blood sample or bone marrow sample.

89. (Currently Amended) The method of claim 68, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of the genomic nucleic acids.

90. (Cancelled)

91. (Cancelled)

92. (Currently Amended) The method of ~~claim 90~~claim 89, wherein the nucleic acid tags are six nucleotides long.

93. (Cancelled)

94. (Previously Presented) The method of claim 89, wherein the nucleic acid tags vary in length.

95. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

96. (Withdrawn) The method of claim 95, wherein the length of the constant portions and the length of the variable portions is the same.

97. (Currently Amended) The method of claim 95, wherein the length of the constant portions and the length of the variable portions ~~is~~ are different.

98. (Withdrawn) The method of claim 95, wherein the variable portions consist of only two species of nucleotides.

99. (Previously Presented) The method of claim 95, wherein the variable portions consist of only three species of nucleotides.

100. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed from a set of dinucleotides.

101. (Withdrawn) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed from a set of trinucleotides.

102-104. (Cancelled)

105. (Currently Amended) The method of claim 68, wherein the nucleic acid tags ~~used to tag the segments of genomic nucleic acids in step b)~~ comprise a sufficiently large number of distinct nucleic acid tags to generate unique tagged nucleic acid molecules.

106. (Currently Amended) The method of claim 105, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of the genomic nucleic acids.

107. (Cancelled)

108. (Cancelled)

109. (Currently Amended) The method of ~~claim 107~~claim 106, wherein the nucleic acid tags are six nucleotides long.

110. (Cancelled)

111. (Previously Presented) The method of claim 105, wherein the nucleic acid tags vary in length.

112. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

113. (Withdrawn) The method of claim 112, wherein the length of the constant portions and the length of the variable portions is the same.

114. (Currently Amended) The method of claim 112, wherein the length of the constant portions and the length of the variable portions ~~is~~ are different.

115. (Withdrawn) The method of claim 112, wherein the variable portions consist of only two species of nucleotides.

116. (Previously Presented) The method of claim 112, wherein the variable portions consist of only three species of nucleotides.

117. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed from a set of dinucleotides.

118. (Withdrawn) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed from a set of trinucleotides.

119. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences that are not known prior to generating tagged nucleic acid molecules.

120. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise random nucleotide sequences.

121. (Previously Presented) The method of claim 105, wherein the nucleic acid tags are substantially unique nucleic acid tags.

122. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are substantially unique nucleic acid tags.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

405 Lexington Avenue
48th Floor
New York, NY 10174
May 9, 2024

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO NOVEMBER 9, 2023 FINAL OFFICE ACTION AS A SUBMISSION UNDER 37 C.F.R. § 1.114 ACCOMPANYING A REQUEST FOR CONTINUED EXAMINATION (RCE), SUMMARY OF MARCH 27, APRIL 8 AND MAY 7, 2024 EXAMINER INTERVIEWS, AND PETITION FOR THREE-MONTH EXTENSION OF TIME

This Amendment is a submission under 37 C.F.R. §1.114 accompanying a Request for Continued Examination (RCE) and responds to the issues raised in a November 9, 2023 Final Office Action issued in connection with the above-identified application. A response to the November 9, 2023 Office Action was originally due February 9, 2024. Applicants hereby petition for a three-month extension of time. The fee for a three-month extension of time is five hundred ninety two dollars ($592.00) for a small entity and authorization is hereby given to charge this amount to a credit card linked to Customer Number 1912. With a three-month extension of time, a response is now due May 9, 2024. Accordingly, this Amendment and the accompanying RCE are being timely filed.

Amendments to the Claims begin on page **2** of this paper.
A **Summary of the March 27, April 8 and May 7, 2024 Examiner Interviews** begins on page **8** of this paper.
Remarks begin on page **9** of this paper.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 05/10/2024

Gary J. Gershik; John P. White
405 LEXINGTON AVENUE
NEW YORK, NY 10174

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
05/10/2024	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):

PTODOCKET@ARELAW.COM
klees@ARELAW.com
patcomm-in-grp@cooperdunham.com

Applicant-Initiated Interview Summary	**Application No.** 16/269,818	**Applicant(s)** Hicks et al.		
	Examiner FRANK W LU	**Art Unit** 1634	**AIA (First Inventor to File) Status** No	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
FRANK W LU	Primary Examiner	Video Conference
Mr.Gary Gershik (Reg.No.39,992)	Attorney of Record	
Mr.Darren Haber		
Dr. Vlad Drozdoff		

Date of Interview: 07 May 2024

Issues Discussed:

Proposed Amendment(s)

Applicant's representatives and the examiner discussed the rejections and possible amendments.
Applicant will file a response

/FRANK W LU/ Primary Examiner, Art Unit 1634	May 7, 2024

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	**05/14/2024 10:45:21 AM Z ET**	**81503-AAA/GJG/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	65513886	FILING DATE	02/07/2019
CUSTOMER #	23432	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 5

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
240514_81503-AAA_IDS3_DH.pdf		5	-	338 KB
240514_81503-AAA_IDS3_DH-TRAN.LET.pdf	(1-2)	2	Transmittal Letter	130 KB
240514_81503-AAA_IDS3_DH-PTA.IDS.pdf	(3-3)	1	Patent Term Adjustment Statement under 37 CFR 1.704(d) filed with an IDS	115 KB
240514_81503-AAA_IDS3_DH-TRAN.LET.pdf	(4-4)	1	Transmittal Letter	127 KB

240514_81503-AAA_IDS3_DH-IDS.pdf	(5-5)	1	Information Disclosure Statement (IDS) Form (SB08)	298 KB
240514_81503-AAA_IDS3_Exh1_DH.pdf		11	Other reference-Patent/Application/Search Documents	398 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

405 Lexington Avenue
New York, NY 10174
May 14, 2024

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

THIRD INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, applicants direct the Examiner's attention to the following items listed below which are also listed on the Substitute Form PTO-1449 attached hereto as **Exhibit A.**

This Information Disclosure Statement is being submitted pursuant to 37 C.F.R. § 1.97(b)(4) before the mailing of a first office action after the filing of a request for continued examination under § 1.114 and no fee is deemed necessary with the filing of this Information Disclosure Statement. Thus, this Information Disclosure Statement should be entered and considered.

A copy of item **1** is attached hereto as **Exhibit 1.**

1. April 30, 2024 extended European search report issued in connection with European Patent Application No. 23197909.7 (**Exhibit 1**)

The April 30, 2024 extended European search report submitted as Exhibit 1 cites the following references, which have all been previously disclosed to the United States Patent and Trademark Office as indicated below:

2. U.S. Patent Application Publication No. 2007/172873, published July 26, 2007 (Cite ID No. 31 of First Information Disclosure Statement filed April 19, 2019);

3. U.S. Patent Application Publication No. 2004/110153, published June 10, 2004 (Cite ID No. 37 of First Information Disclosure Statement filed April 19, 2019);

4. PCT International Patent Application Publication No. WO 2007/062445 A1, published June 7, 2007 (Cite ID No. 39 of First Information Disclosure Statement filed April 19, 2019);

5. U.S. Patent Application Publication No. 2010/178655 A1, published July 15, 2010 (Cite ID No. 27 of First Information Disclosure Statement filed April 19, 2019); and

6. Miner et al., "Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR," Nucleic Acids Res. vol. 32 no. 17 (2004), p. 1-4 (Cite ID No. 69 of First Information Disclosure Statement filed April 19, 2019).

The Examiner is respectfully requested to make of record each item listed on the Form PTO-1449 Substitute by initialing and dating the attached Form PTO-1449 Substitute and returning a copy of the initialed and dated form to applicants' undersigned attorney.

Statement under 37 C.F.R. § 1.704(d)(1)

In accordance with 37 C.F.R. § 1.704(d)(1), applicants hereby state that the April 30, 2024 extended European search report issued in connection with European Patent Application No. 23197909.7 is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of this information disclosure statement.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

Gary J. Gershik
Registration No. 39,992
Attorney for Applicants
Amster, Rothstein & Ebenstein LLP
405 Lexington Avenue
New York, NY 10174
(212) 336-8000

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on May 14, 2024.

/Darren Haber/

Darren Haber

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No.	Application No.
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		81503-AAA/GJG/DH	16/269,818
		First Named Inventor: James Hicks	Confirmation Number: 8088
		Filing Date: February 7, 2019	Group Art Unit: 1634

NON PATENT LITERATURE DOCUMENTS		
Examiner Initial	Cite ID[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.
	1	April 30, 2024 extended European search report issued in connection with European Patent Application No. 23197909.7

Examiner Signature	Date Considered

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Substitute Disclosure Form (PTO-1449)

Third Information Disclosure Statement

EXHIBIT A

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/269,818	Filing Date 02/07/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	09/20/2024	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 36	Minus	** 47	= 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

		(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 $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.	Non-Examiner
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/RICARDO ANTONIO CAMOU/
*** 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.

REMARKS

In this Supplemental Amendment, applicant has amended claims 68, 72, 100, 101, 105, 117, 118, and 119. Support for the amendment to claim 68 may be found in the subject specification, *inter alia*, on page 48, lines 20-25. Claims 72, 100, 101, 105, 117, 118, and 119 have been amended for improved clarity.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Supplemental Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

Gary J. Gershik
Registration No. 39,992
Amster Rothstein & Ebenstein LLP
405 Lexington Avenue
48th Floor
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(212) 336-8000

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on September 20, 2024.

/Darren Haber/

Darren Haber
Reg. No. 80,964

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 #
16/269,818	**09/20/2024 05:26:59 PM Z ET**	**81503-AAA/GJG/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	67264702	FILING DATE	02/07/2019
CUSTOMER #	23432	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
240920_81503-AAA_SupplementalAmendment_DH.pdf		7	-	156 KB
240920_81503-AAA_SupplementalAmendment_DH-SA...pdf	(1-1)	1	Supplemental Response or Supplemental Amendment	85 KB
240920_81503-AAA_SupplementalAmendment_DH-CLM.pdf	(2-6)	5	Claims	125 KB
240920_81503-AAA_SupplementalAmendment_DH-REM.pdf	(7-7)	1	Applicant Arguments/Remarks Made in an Amendment	138 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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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.

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1-67. (Cancelled).

68. (Currently Amended) A method comprising:

a) obtaining segments of genomic nucleic acids from a sample containing the genomic nucleic acids;

b) randomly tagging the segments of genomic nucleic acids with different nucleic acid tags, thereby generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;

c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating amplified unique tagged nucleic acid molecules;

d) generating tag associated sequence reads by sequencing the amplified unique tagged nucleic acid molecules of step (c);

e) assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and

f) in a plurality of locations in the genome, obtaining relative copy number information of the genomic nucleic acids from the sample based on ~~a count of~~ the number of unique tagged nucleic acid molecules that have been assigned to each of the plurality of ~~the same~~ locations in the genome.

69-70. (Cancelled).

71. (Previously Presented) The method of claim 68, wherein the polymerase chain reaction is performed in the presence of region specific PCR primers.

72. (Currently Amended) The method of claim 68, wherein the unique tagged nucleic acid molecules differ at more than one nucleotide or wherein the sequences of the nucleic acid tags are known prior to said generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids.

73. (Previously Presented) The method of claim 68, wherein the segments of the genomic nucleic acids are produced by mechanical shearing, heating, or sonicating the genomic nucleic acids from the sample.

74. (Previously Presented) The method of claim 68, wherein the nucleic acid tags comprise a sample tag or a sample tag set.

75. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are double-stranded.

76-83. (Cancelled)

84. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to the PCR or the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d).

85. (Previously Presented) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR or prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c).

86. (Previously Presented) The method of claim 85, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads.

87. (Previously Presented) The method of claim 68, wherein the genomic nucleic acids are from a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

88. (Previously Presented) The method of claim 68, wherein the sample is a blood sample or bone marrow sample.

89. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of the genomic nucleic acids.

90. (Cancelled)

91. (Cancelled)

92. (Previously Presented) The method of claim 89, wherein the nucleic acid tags are six nucleotides long.

93. (Cancelled)

94. (Previously Presented) The method of claim 89, wherein the nucleic acid tags vary in length.

95. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

96. (Withdrawn) The method of claim 95, wherein the length of the constant portions and the length of the variable portions is the same.

97. (Previously Presented) The method of claim 95, wherein the length of the constant portions and the length of the variable portions are different.

98. (Withdrawn) The method of claim 95, wherein the variable portions consist of only two species of nucleotides.

99. (Previously Presented) The method of claim 95, wherein the variable portions consist of only three species of nucleotides.

100. (Currently Amended) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed by [[from]] a set of dinucleotides.

101. (Withdrawn – Currently Amended) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed by [[from]] a set of trinucleotides.

102-104. (Cancelled)

105. (Currently Amended) The method of claim 68, wherein the nucleic acid tags comprise a sufficiently large number of distinct nucleic acid tags~~ to generate unique tagged nucleic acid molecules~~.

106. (Previously Presented) The method of claim 105, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of the genomic nucleic acids.

107. (Cancelled)

108. (Cancelled)

109. (Previously Presented) The method of claim 106, wherein the nucleic acid tags are six nucleotides long.

110. (Cancelled)

111. (Previously Presented) The method of claim 105, wherein the nucleic acid tags vary in length.

112. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

113. (Withdrawn) The method of claim 112, wherein the length of the constant portions and the length of the variable portions is the same.

114. (Previously Presented) The method of claim 112, wherein the length of the constant portions and the length of the variable portions are different.

115. (Withdrawn) The method of claim 112, wherein the variable portions consist of only two species of nucleotides.

116. (Previously Presented) The method of claim 112, wherein the variable portions consist of only three species of nucleotides.

117. (Currently Amended) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed by [[from]] a set of dinucleotides.

118. (Withdrawn - Currently Amended) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed by [[from]] a set of trinucleotides.

119. (Currently Amended) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences that are not known ~~prior to generating~~ before the tagged nucleic acid molecules are generated.

120. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise random nucleotide sequences.

121. (Previously Presented) The method of claim 105, wherein the nucleic acid tags are substantially unique nucleic acid tags.

122. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are substantially unique nucleic acid tags.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	: Cold Spring Harbor Laboratory		
U.S. Serial No.	: 16/269,818	Examiner	: Frank Lu
Filing Date	: February 7, 2019	Art Unit	: 1634
Confirmation No.	: 8088		
For	: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION		

405 Lexington Avenue
48th Floor
New York, NY 10174
September 20, 2024

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT

This Supplemental Amendment is being filed before the issuance of an Office Action following Applicant's filing of an Amendment and Request for Continued Examination (RCE) on May 9, 2024.

Amendments to the Claims begin on page **2** of this paper.
Remarks begin on page **7** of this paper.

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L5509	4	(fragment OR segment) SAME genomic NEAR (DNA OR polynucleotide OR "nucleic acid") SAME (tag OR tagging) SAME (PCR OR "polymerase chain reaction") SAME sequence NEAR read SAME (location OR region) near3 genome SAME relative NEAR copy NEAR number	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/09/27 11:49 PM
L5510	14	(fragment OR segment) SAME genomic NEAR (DNA OR polynucleotide OR "nucleic acid") SAME (tag OR tagging) SAME (PCR OR "polymerase chain reaction") SAME sequence NEAR read SAME genome SAME relative NEAR copy NEAR number	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/09/27 11:50 PM
L5511	155	(fragment OR segment) SAME genomic NEAR (DNA OR polynucleotide OR "nucleic acid") SAME (tag OR tagging) SAME (PCR OR "polymerase chain reaction") SAME sequence NEAR read SAME genome SAME copy NEAR number	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/09/27 11:50 PM
L5512	155	(fragment OR segment) SAME genomic NEAR (DNA OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY,	OR	ON	ON	2024/09/27 11:50 PM

IPR2025-01353
CSHL EX2001

		polynucleotide OR "nucleic acid") SAME (tag OR tagging) SAME (PCR OR "polymerase chain reaction") SAME sequence NEAR read SAME genome SAME copy NEAR number	CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)				
L5513	74	(fragment OR segment) SAME genomic NEAR (DNA OR polynucleotide OR "nucleic acid") SAME (tag OR tagging) SAME (PCR OR "polymerase chain reaction") SAME sequence NEAR read SAME (location OR region) near3 genome SAME copy NEAR number	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/09/27 11:51 PM
L5514	72	L5513 AND ((B01L2200/027 OR B01L2200/10 OR B01L2200/16 OR B01L2300/0654 OR B01L2300/0672 OR B01L2300/0681 OR B01L2300/0816 OR B01L2300/0867 OR B01L2300/0874 OR B01L2300/0887 OR B01L2300/123 OR B01L2300/1822 OR B01L2400/0421 OR B01L2400/043 OR B01L2400/0481 OR B01L2400/0487 OR B01L2400/0655 OR B01L3/502715 OR B01L3/527 OR B01L7/52 OR C12N15/1065 OR C12N15/113 OR C12N2310/14 OR C12N15/102 OR C12N15/1093 OR C07K16/18 OR A61N5/1064 OR	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/09/27 11:52 PM

IPR2025-01353
GSHL EX2001

		A61K31/713 OR A61K45/06 OR G06F18/24155 OR G06F17/10 OR G06F17/11 OR G06F16/9035 OR C40B30/00 OR C40B70/00 OR G06N7/01 OR G01N33/50 OR G01N2458/10 OR G01N33/57484 OR G01N33/68 OR G01N2800/245 OR G01N2469/20 OR G01N33/54326 OR G01N33/57434 OR Y02A90/10 OR Y02A50/30 OR G16H10/40 OR G16H50/30 OR G16H50/20 OR G16H50/70 OR G16B20/00 OR G16B30/00 OR G16B20/10 OR G16B20/20 OR G16B25/00 OR G16B30/10 OR G16B20/40 OR G16B40/00 OR G16B5/00 OR G16B30/20 OR G16B40/20 OR G16B5/20 OR G16B25/20 OR G16B99/00 OR G16B45/00 OR G16B25/10 OR G16B40/30 OR G16B50/00 OR G16B50/30 OR C12Q2600/156 OR C12Q1/6869 OR C12Q1/6886 OR C12Q1/6874 OR C12Q1/6881 OR C12Q1/6883 OR C12Q1/6827 OR C12Q1/683 OR C12Q1/6806 OR C12Q1/6809 OR C12Q1/686 OR C12Q2600/16 OR C12Q2535/122 OR C12Q2537/16 OR C12Q1/6855 OR C12Q2525/155 OR					

		C12Q2537/159 OR C12Q2525/191 OR C12Q2537/143 OR C12Q2537/149 OR C12Q2545/114 OR C12Q1/6804 OR C12Q2600/112 OR C12Q2563/179 OR C12Q1/6876 OR C12Q2537/165 OR C12Q2600/106 OR C12Q2600/172 OR C12Q1/6844 OR C12Q1/6851 OR C12Q1/6862 OR C12Q1/6872 OR C12Q2525/179 OR C12Q2527/113 OR C12Q2527/143 OR C12Q2537/161 OR C12Q2600/154 OR C12Q1/68 OR C12Q1/70 OR C12Q2531/113 OR C12Q2545/101 OR C12Q1/6879 OR C12Q1/689 OR C12Q1/6816 OR C12Q1/6837 OR C12Q1/6853 OR C12Q1/6888 OR C12Q2521/301 OR C12Q2521/501 OR C12Q2535/119 OR C12Q2600/118 OR C12Q2600/158 OR C12Q2600/166).cpc.)					

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	Art Unit
	FRANK W LU	1634

CPC - Searched*		
Symbol	Date	Examiner
Update	09/27/2024	/FL/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
Update	09/27/2024	/FL/

US Classification - Searched*			
Class	Subclass	Date	Examiner
Update		09/27/2024	/FL/

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Update (see attached file)	09/27/2024	/FL/

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

/FRANK W LU/ Primary Examiner, Art Unit 1634	September 27, 2024

IPR2025-01353
GSHL 2002001

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No.	Application No.
		81503-AAA/GJG/DH	16/269,818
Information Disclosure Statement by Applicant (Use several sheets if necessary)		First Named Inventor: James Hicks	Confirmation Number: 8088
		Filing Date: February 7, 2019	Group Art Unit: 1634
(37 CFR §1.98(b))			

NON PATENT LITERATURE DOCUMENTS		
Examiner Initial	Cite ID[1]	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, page(s), volume-issue number(s), publisher, city and/or country where published.
	1	April 30, 2024 extended European search report issued in connection with European Patent Application No. 23197909.7

Examiner Signature	Date Considered
/FRANK W LU/	09/29/2024

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Substitute Disclosure Form (PTO-1449)

Third Information Disclosure Statement

EXHIBIT A

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /F.W.L/

IPR2025-01353
CSHL EX2001

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 09/30/2024

Gary J. Gershik; John P. White
405 LEXINGTON AVENUE
NEW YORK, NY 10174

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
09/30/2024	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):

PTODOCKET@ARELAW.COM
klees@ARELAW.com
patcomm-in-grp@cooperdunham.com

Office Action Summary	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	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 5/9/2024 and 9/20/2024.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 68,71-75,84-89,92,94-101,105-106,109 and 111-122 is/are pending in the application.

5a) Of the above claim(s) 96,98,101,113,115 and 118 is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 68,71-75,84-89,92,94-95,97,99-100,105-106,109,111-112,114,116-117 and 119-122 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 2/7/2019 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 5/14/2024.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

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 of RCE filed on May 9, 2024 and the amendments filed on May 9, 2024 and September 20, 2024 have been entered. The claims pending in this application are claims 68, 71-75, 84-89, 92, 94-101, 105, 106, 109, and 111-122 wherein claims 96, 98, 101, 113, 115, and 118 have been withdrawn due to the election of species mailed on August 10, 2023. Rejections and/or objections not reiterated from the previous office action are hereby withdrawn in view of applicant's amendment filed on May 9, 2024 and September 20, 2024. Claims 68, 71-75, 84-89, 92, 94, 95, 97, 99, 100, 105, 106, 109, 111, 112, 114, 116, 117, and 119-122 will be examined.

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 68, 71-75, 84-89, 92, 94, 95, 97, 99, 100, 105, 106, 109, 111, 112, 114, 116, 117, and 119-122 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.

4. Claim 68 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: comparing a count of the number of the amplified unique tagged nucleic acid that have been assigned to each of the plurality of the locations in the genome because the specification clearly shows that "[101] In an embodiment, the method further comprises comparing a count obtained in step (f) for a location on the genome to a count for the same location obtained from a reference sample, thereby estimating a relative genomic copy number of the location. [0102] In an embodiment, the method further comprises [0103] a) summing the counts obtained in step (f) for locations on the genome which comprise a first region of the genome, wherein the first region comprises more than one location; [0104] b) summing the counts obtained in step (f) for locations on the genome which comprise a second region of the genome, wherein the second region is comprised of a number of locations which is comparable to the number of locations of the first region; [0105] c) comparing the value obtained in step (a) to the value obtained in step (b), [0106] thereby estimating the relative genomic copy number of the first region of the genome to the genomic copy number of the second region. of the genome" (see US 2019/0153535 A1, which is US Publication of this instant case) and without above comparing step, relative copy number information of the genomic nucleic acid from the sample in step f) cannot be obtained.

5. Claim 68 is rejected as vague and indefinite in view of step f). Although step e) requires assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome,

step f) requires assigning the unique tagged nucleic acid molecules in step c) to each of a plurality of locations in the genome, steps e) and f) do not correspond each other. Please clarify.

Response to Arguments

6. Applicant's arguments with respect to claims 68, 71-75, 82-89, 92, 94, 95, 97, 99, 100, 102-106, 109, 111, 112, 114, 116, 117, and 119-122 have been considered but are moot because the new ground of rejection does not rely on any reference applied in the prior rejection of record for any teaching or matter specifically challenged in the argument.

Conclusion

7. No claim is allowed.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen, Ph.D., can be reached on (571)272-3157.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
September 30, 2024

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/269,818	Filing Date 02/07/2019	☐ 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 $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $230 =	
☐ 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	10/22/2024	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 36	Minus	** 47	= 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

		(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 $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".	/KIM R WATSON/
*** 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.

REMARKS

In this amendment, applicant has amended claim 68 solely to clarify the wording of the claim, as discussed in more detail below.

Claim Rejections – 35 U.S.C. § 112 (indefiniteness)

In the September 30, 2024 Office Action, the Examiner rejected claims 68, 71-75, 84-89, 92, 94, 95, 97, 99, 100, 105, 106, 109, 111, 112, 114, 116, 117, and 119-122 under 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly indefinite.

First, the Examiner alleged that claim 68 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Examiner alleged that the omitted step is "comparing a count of the number of the amplified unique tagged nucleic acid that have been assigned to each of the plurality of the locations in the genome". The Examiner alleged that "without above comparing step, relative copy number information of the genomic nucleic acid from the sample in step f) cannot be obtained".

Second, the Examiner alleged that claim 68 is indefinite because steps e) and f) allegedly do not correspond to each other. The Examiner alleged that step e) requires assigning each of the amplified unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome and step f) requires assigning the unique tagged nucleic acid molecules in step c) to each of a plurality of locations in the genome.

Applicant's response

In response, Applicant respectfully traverses the Examiner's rejection because the rejection does not meet the legal criteria for such rejection.

I. Alleged omission of essential steps.

The rejection of Claim 68 under 35 U.S.C. 112 (pre-AIA), second paragraph, as allegedly indefinite for omitting essential steps, does not meet the requirements of such rejection, which are discussed for

example in MPEP § 2171.01. Rejections under pre-AIA 35 U.S.C. 112, second paragraph, based on an "alleged omission of essential matter must explain the basis for concluding that **the inventor regards the omitted matter to be essential** to the invention." *See, e.g., Ex parte Robertson,* Appeal 2016-001938, op. at 4 (PTAB 2017) (Rejection reversed because Examiner failed to identify **where** in the specification the unclaimed elements were **described as essential**. The Board noted that the summary of the invention in the specification did not include features alleged by Examiner to be essential.)

First, the Examiner has not cited any support for the assertion that the alleged omitted subject matter is "essential." In the rejection, the Examiner alleged that the purported "essential" step is "comparing a count of the number of the amplified unique tagged nucleic acid that have been assigned to each of the plurality of the locations in the genome," and cited paragraphs [0101]-[0106] of the specification as published. Paragraphs [0101]-[0106] describe "**embodiments**" of the invention which teach "comparing" counts. However, nothing in these paragraphs nor other parts of the specification describe "comparing" as an essential step.

Accordingly, the record lacks any basis for supporting a rejection to purportedly omitting essential elements.

Second, the rejection has ignored the fact that the paragraphs cited (paragraphs of [0101]-[0106] of the specification as published) describe merely **one** possible method for "obtaining relative genomic copy number information". In this *one particular* method, relative copy number of a "first region" of the genome is obtained by comparing the number of unique tagged nucleic acid molecules that have been assigned to locations within the first region with the number of unique tagged nucleic acid molecules that have been assigned to a second region comprising a comparable number of locations. However, *other methods* of "obtaining relative genomic copy number information" are described in the specification – for example at paragraph [0111], where relative copy number of a region of the genome is obtained by summing the

counts of unique tagged nucleic acid molecules that have been assigned to locations within the region of the genome and comparing this sum to a sum obtained from the same region in a reference sample; or for example at paragraph [0280] which states "[t]he relative copy number of a region can be estimated by comparing the total number of different tagged nucleic acid molecules mapped to the region to, **for example**, the mean value of tagged nucleic acid molecules mapped to other regions of the genome which have a comparable number of locations." (emphasis added). Thus, it is clear that the description cited to support the rejection at [0101]-[0106] is not the only description in the specification for "obtaining relative genomic copy number information."

Accordingly, the description cited to support the rejection at [0101]-[0106] is not essential for "obtaining relative genomic copy number information."

Third, a person of ordinary skill in the art (POSA) reading the specification of the subject application would readily appreciate that "relative genomic copy number information" can be obtained in a variety of ways and, generally, is obtained when the unique tag associated sequence reads have been mapped to each of a plurality of locations in the genome.

Indeed, paragraph [0323] of the specification makes clear that a comparison step is **not** required for "relative copy number information" to be obtained. Paragraph [0323] explains that "the invention may be used to generate a **genomic profile** of a cell, e.g. a cancer cell, or a population of cells. From the genomic profile it can be determined if specific genes are amplified or deleted." (emphasis added). Paragraph [0323] further explains that "[w]hen the sample is derived from expressed RNA, and the regions are expressed genes, **the relative counts comprise an expression profile**" (emphasis added). Thus, this paragraph makes clear that "relative counts" which comprise an "expression profile" can be produced without the need for a comparison step. Analogously, a POSA would appreciate that when the sample is

derived from genomic nucleic acids (rather than expressed RNA as discussed in paragraph [0323]), the relative counts obtained for plurality of locations comprise the genomic profile of a cell, similarly with no comparison step being required.

Therefore, the POSA would readily appreciate that the specification provides multiple ways for "obtaining relative genomic copy number information" and that nothing essential is omitted from the claim.

II. Correspondence of steps e) and f):

Regarding the Examiner's allegation that steps e) and f) do not correspond to each other, applicant has amended step c) to clarify that the step generates "copies of the unique tagged nucleic acid molecules". Similarly, applicant has amended step d) to clarify that tag associated sequence reads are generated by sequencing the copies of the unique tagged nucleic acid molecules. Further, step e) now recites assigning each of the unique tagged nucleic acid molecules to a location on a genome based on mapping each of the tag associated sequence reads of step d) to a location in the genome.

As amended, the language regarding "assigning each of the unique tagged nucleic acid molecules to a location on a genome" in step e) corresponds directly to the language of step f) which recites obtaining relative copy number information of the genomic nucleic acids from the sample "based on the number of unique tagged nucleic acid molecules that have been assigned" to each of a plurality of locations in the genome.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

_____

Gary J. Gershik
Registration No. 39,992
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Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on October 22, 2024.

/Darren Haber/

_____

Darren Haber

Reg. No. 80,964

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	**10/22/2024 06:28:32 PM Z ET**	**81503-AAA/GJG/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	67677327	FILING DATE	02/07/2019
CUSTOMER #	23432	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
241022_81503-AAA_Amendment_DH.pdf		12	-	184 KB
241022_81503-AAA_Amendment_DH-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	90 KB
241022_81503-AAA_Amendment_DH-CLM.pdf	(2-6)	5	Claims	130 KB
241022_81503-AAA_Amendment_DH-REM.pdf	(7-12)	6	Applicant Arguments/Remarks Made in an Amendment	166 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
241022_81503-AAA_Amendment_DH.pdf	7EDAAC1FC18B61B3D328DFB443BB208E9E93B01933824CC51159F9465A011FBEE6E659A892040131DCF91E8140DF4B93F09D4601737B8CFD8A875F0DB9067A91
241022_81503-AAA_Amendment_DH-A....pdf	00BBED85D2BBE221D7854822081BA1068064EA73DA43F94D1A4BAFE75A73C1BF3CB2AA83882A707D35B4BEF218C6F3F3740E9A78A2F876172179CC54E37DD4C4
241022_81503-AAA_Amendment_DH-CLM.pdf	D81F9CFC44CFAC717496F5C400EAFDDE6EFB863D1289101C6A04E6E956E378F0760B7A4A150F419BC7F4CAC1D62CE661AEFDF88BF209BDAEF4E47EBA4BF07FE2
241022_81503-AAA_Amendment_DH-REM.pdf	D78DF0ACBD15ACE2808F47AD35BAD12D4F8D89574CB760E81D34E5E92814600E8AD3D5F468FC5267454F4F14A9348034963D3B8FB2DD45698CC996D1442D866E

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.

AMENDMENTS TO THE CLAIMS

Pursuant to 37 C.F.R. § 1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1-67. (Cancelled).

68. (Currently Amended) A method comprising:

a) obtaining segments of genomic nucleic acids from a sample containing the genomic nucleic acids;

b) randomly tagging the segments of genomic nucleic acids with different nucleic acid tags, thereby generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;

c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating ~~amplified~~ copies of the unique tagged nucleic acid molecules;

d) generating tag associated sequence reads by sequencing the ~~amplified~~ copies of the unique tagged nucleic acid molecules of step (c);

e) assigning each of the ~~amplified~~ unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and

f) in a plurality of locations in the genome, obtaining relative copy number information of the genomic nucleic acids from the sample based on the number of unique tagged nucleic acid molecules that have been assigned to each of the plurality of locations in the genome.

69-70. (Cancelled).

71. (Previously Presented) The method of claim 68, wherein the polymerase chain reaction is performed in the presence of region specific PCR primers.

72. (Currently Amended) The method of claim 68, wherein the unique tagged nucleic acid molecules differ at more than one nucleotide or wherein the sequences of the nucleic acid tags are known prior to said generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids.

73. (Previously Presented) The method of claim 68, wherein the segments of the genomic nucleic acids are produced by mechanical shearing, heating, or sonicating the genomic nucleic acids from the sample.

74. (Previously Presented) The method of claim 68, wherein the nucleic acid tags comprise a sample tag or a sample tag set.

75. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are double-stranded.

76-83. (Cancelled)

84. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to the PCR or the amplified tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d).

85. (Previously Presented) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR or prior to said sequencing of the amplified tagged nucleic acid molecules product of step (c).

86. (Previously Presented) The method of claim 85, further comprising deconvoluting the tag associated sequence reads by grouping the tag associated sequence reads.

87. (Previously Presented) The method of claim 68, wherein the genomic nucleic acids are from a single species, a single cell, two or more organisms, two or more species, or from a population of microbes.

88. (Previously Presented) The method of claim 68, wherein the sample is a blood sample or bone marrow sample.

89. (Previously Presented) The method of claim 68, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of the genomic nucleic acids.

90. (Cancelled)

91. (Cancelled)

92. (Previously Presented) The method of claim 89, wherein the nucleic acid tags are six nucleotides long.

93. (Cancelled)

94. (Previously Presented) The method of claim 89, wherein the nucleic acid tags vary in length.

95. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

96. (Withdrawn) The method of claim 95, wherein the length of the constant portions and the length of the variable portions is the same.

97. (Previously Presented) The method of claim 95, wherein the length of the constant portions and the length of the variable portions are different.

98. (Withdrawn) The method of claim 95, wherein the variable portions consist of only two species of nucleotides.

99. (Previously Presented) The method of claim 95, wherein the variable portions consist of only three species of nucleotides.

100. (Currently Amended) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed by a set of dinucleotides.

101. (Previously Presented) The method of claim 89, wherein the nucleic acid tags comprise variable portions constructed by a set of trinucleotides.

102-104. (Cancelled)

105. (Previously Presented) The method of claim 68, wherein the nucleic acid tags comprise a sufficiently large number of distinct nucleic acid tags.

106. (Previously Presented) The method of claim 105, wherein the unique tagged nucleic acid molecules are unique based on a combination of sequence information in the nucleic acid tags and sequence information in the segments of the genomic nucleic acids.

107. (Cancelled)

108. (Cancelled)

109. (Previously Presented) The method of claim 106, wherein the nucleic acid tags are six nucleotides long.

110. (Cancelled)

111. (Previously Presented) The method of claim 105, wherein the nucleic acid tags vary in length.

112. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences with constant portions and variable portions.

113. (Withdrawn) The method of claim 112, wherein the length of the constant portions and the length of the variable portions is the same.

114. (Previously Presented) The method of claim 112, wherein the length of the constant portions and the length of the variable portions are different.

115. (Withdrawn) The method of claim 112, wherein the variable portions consist of only two species of nucleotides.

116. (Previously Presented) The method of claim 112, wherein the variable portions consist of only three species of nucleotides.

117. (Currently Amended) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed by a set of dinucleotides.

118. (Withdrawn) The method of claim 105, wherein the nucleic acid tags comprise variable portions constructed by a set of trinucleotides.

119. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise nucleotide sequences that are not known before the tagged nucleic acid molecules are generated.

120. (Previously Presented) The method of claim 105, wherein the nucleic acid tags comprise random nucleotide sequences.

121. (Previously Presented) The method of claim 105, wherein the nucleic acid tags are substantially unique nucleic acid tags.

122. (Previously Presented) The method of claim 68, wherein the nucleic acid tags are substantially unique nucleic acid tags.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Cold Spring Harbor Laboratory

U.S. Serial No. : 16/269,818 Examiner : Frank Lu

Filing Date : February 7, 2019 Art Unit : 1634

Confirmation No. : 8088

For : VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

405 Lexington Avenue
48th Floor
New York, NY 10174
October 22, 2024

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO SEPTEMBER 30, 2024 OFFICE ACTION

This Amendment is submitted in response to the September 30, 2024 Office Action issued in connection with the above-identified application. A response to the September 30, 2024 Office is due December 30, 2024. Accordingly, this Amendment is being timely filed.

Amendments to the Claims begin on page **2** of this paper.
Remarks begin on page **7** of this paper.

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L6319	7	(fragment OR segment) SAME genomic NEAR (DNA OR polynucleotide OR "nucleic acid") SAME (tag OR tagging OR adaptor OR adapter OR linker) SAME (PCR OR "polymerase chain reaction") SAME sequence NEAR read SAME genome SAME (map OR mapping) SAME relative NEAR copy NEAR number	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/12/23 07:59 PM
L6320	7	L6319 AND ((C12Q2600/156 OR C12Q1/6883 OR C12Q1/683 OR C12Q1/6869 OR C12Q1/6874 OR C12Q1/6881 OR C12Q1/6886 OR C12Q2600/106 OR G16B25/00 OR C07K14/47 OR C07K14/4728 OR C07K14/705 OR C07K16/2842 OR C12N9/20 OR C12N9/93 OR C12N15/111 OR C12N2310/141 OR C12N2320/10 OR G01N2500/04 OR G01N2800/2814 OR G01N33/6896 OR G01N2800/38 OR G01N33/6845 OR Y02A50/30).cpc.)	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2024/12/23 08:00 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	Art Unit
	FRANK W LU	1683

CPC - Searched*		
Symbol	Date	Examiner
Update	12/23/2024	/FL/

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
Update	12/23/2024	/FL/

US Classification - Searched*			
Class	Subclass	Date	Examiner
Update		12/23/2024	/FL/

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Update (see attached file)	12/23/2024	/FL/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
CPC C12Q	1/683, 6874, 6881, 6886; 2525/155,196; 2535/122; 2537/16,159; 2600/156	12/23/2024	/FL/
CPC G16B	15/00	12/23/2024	/FL/

/FRANK W LU/ Primary Examiner, Art Unit 1634	December 23, 2024

IPR2025-01353
GSK-2002

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	**Art Unit**
	FRANK W LU	1683

CPC							
Symbol						**Type**	**Version**
C12Q	/	1	/	6874		F	2013-01-01
G16B	/	25	/	00		I	2019-02-01
C12Q	/	1	/	6886		I	2013-01-01
C12Q	/	1	/	683		I	2013-01-01
C12Q	/	1	/	6881		I	2013-01-01
C12Q	/	2600	/	156		A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
C12Q	/	1	/	683	I	1	1	2013-01-01
C12Q	/	2525	/	155	I	1	2	2013-01-01
C12Q	/	2525	/	191	I	1	3	2013-01-01
C12Q	/	2535	/	122	I	1	4	2013-01-01
C12Q	/	2537	/	159	I	1	5	2013-01-01
C12Q	/	2537	/	16	I	1	6	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	36	
/FRANK W LU/ Primary Examiner, Art Unit 1683	23 December 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	**Art Unit**
	FRANK W LU	1683

INTERNATIONAL CLASSIFICATION					
CLAIMED					
C12P	/	19	/	34	
NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
435	91.2

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 36	
/FRANK W LU/ Primary Examiner, Art Unit 1683 (Primary Examiner) 23 December 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/269,818	Hicks et al.
	Examiner	**Art Unit**
	FRANK W LU	1683

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	68	10	87	19	99	28	114								
2	71	11	88	20	100	29	115								
3	72	12	89	21	101	30	116								
4	73	13	92	22	105	31	117								
5	74	14	94	23	106	32	118								
6	85	15	95	24	109	33	119								
7	86	16	96	25	111	34	120								
8	75	17	97	26	112	35	121								
9	84	18	98	27	113	36	122								

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 36	
/FRANK W LU/ Primary Examiner, Art Unit 1683 (Primary Examiner)	23 December 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

Examiner-Initiated Interview Summary	**Application No.** 16/269,818	**Applicant(s)** Hicks et al.		
	Examiner FRANK W LU	**Art Unit** 1683	**AIA (First Inventor to File) Status** No	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
FRANK W LU	Primary Examiner	Telephonic
Mr.Gary Gershik (Reg. No. 39,992)	Attorney of Record	

Date of Interview: 23 December 2024

Issues Discussed:

Proposed Amendment(s)

Mr.Gershik agreed with the examiner's amendment.

/FRANK W LU/ Primary Examiner, Art Unit 1683	December 23, 2024

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

23432 7590 01/13/2025

Gary J. Gershik; John P. White; Paul Teng
AMSTER ROTHSTEIN & EBENSTEIN LLP
405 Lexington Avenue, 48th Floor
New York, NY 10174

EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1683	

DATE MAILED: 01/13/2025

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

TITLE OF INVENTION: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	04/14/2025

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

IPR2025-01353
CSHL EX2001

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23432 7590 01/13/2025

Gary J. Gershik; John P. White; Paul Teng
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405 Lexington Avenue, 48th Floor
New York, NY 10174

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

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EXAMINER	ART UNIT	CLASS-SUBCLASS
LU, FRANK WEI MIN	1683	435-006110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

IPR2025-01353
CSHL EX2001

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 30 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) 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));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 16/269,818	Applicant(s) Hicks et al.	
	Examiner FRANK W LU	Art Unit 1683	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to the amendment filed on 10/22/2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ 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.

3. ☑ The allowed claim(s) is/are See Continuation Sheet . As a result of the allowed claim(s), 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.**

4. ☐ 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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 12/23/2024.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/FRANK W LU/ Primary Examiner, Art Unit 1683	December 23, 2024

Continuation of 3. The allowed claim(s) is/are: 68,71-75,84-89,92,94-101,105-106,109 and 111-122

DETAILED ACTION

Reasons for Allowance

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Gary Gershik (Reg. No.39,992) on December 23, 2024.

2. The application has been amended as follows:

Rejoining claims 96, 98, 113, and 118 with claims 68, 71-75, 84-89, 92, 94, 95, 97, 99-101, 105, 106, 109, 111, 112, 114-117, and 119-122.

68. (Currently Amended) A method comprising:

a) obtaining segments of genomic nucleic acids from a sample containing the genomic nucleic acids;

b) randomly tagging the segments of genomic nucleic acids with different nucleic acid tags, thereby generating unique tagged nucleic acid molecules from the segments of genomic nucleic acids, such that each of the unique tagged nucleic acid molecules comprises a segment of the segments of the genomic nucleic acids from step (a) and a nucleic acid tag of the nucleic acid tags;

c) subjecting the unique tagged nucleic acid molecules to a polymerase chain reaction (PCR), thereby generating copies of the unique tagged nucleic acid molecules;

d) generating tag associated sequence reads by sequencing the copies of the unique tagged nucleic acid molecules of step (c);

e) assigning each of the copies of the unique tagged nucleic acid molecules to a location on a genome by mapping each of the tag associated sequence reads of step (d) to a location in the genome; and

f) in a plurality of locations in the genome, obtaining relative copy number information of the genomic nucleic acids from the sample based on the number of unique tagged nucleic acid molecules that ~~have been~~ are assigned to each of the plurality of locations in the genome.

84. (Currently Amended) The method of claim 68, wherein the unique tagged nucleic acid molecules are subjected to hybrid capture prior to the PCR or the ~~amplified~~ copies of the unique tagged nucleic acid molecules produced in step (c) are subjected to hybrid capture prior to step (d).

85. (Currently Amended) The method of claim 74, wherein the unique tagged nucleic acid molecules are pooled with a plurality of unique tagged nucleic acid molecules having a different sample tag prior to the PCR or prior to said sequencing of the ~~amplified~~ copies of the unique tagged nucleic acid molecules product of step (c).

87. (Currently Amended) The method of claim 68, wherein the genomic nucleic acids are from a single species, a single cell, two or more organisms, two or more species, or ~~from~~ a population of microbes.

3. The following is an examiner's statement of reasons for allowance:

Claims 68, 71-75, 84-89, 92, 94-101, 105, 106, 109, and 111-122 are allowable in light of applicant's amendment filed on October 22, 2024, the terminal disclaimer filed on June 2, 2023, and the examiner's amendment. The rejections under 35 U.S.C. 112 (b) have been withdrawn in view of applicant's arguments (see pages 7, fifth paragraph bridging to page 10, last paragraph of applicant's remarks) filed on October 22, 2024. The closest prior arts in the record are Casbon *et*

al., (US 8, 715,967 B2, priority date: September 21, 2010) and Xie *et al.,* (BMC Bioinformatics, 10, 80, March 6, 2009). There prior arts do not teach a combination of steps a) to f) of claim 68. These prior arts either alone or in combination with the other art in the record do not teach or reasonably suggest a method which comprises all of the limitations recited in claim 68.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance".

4. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Cynthia Wilder, Ph.D., can be reached on (571)272-0791.

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.

/FRANK W LU/
Primary Examiner, Art Unit 1634
December 23, 2024

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 #
16/269,818	**01/15/2025 04:01:02 PM Z ET**	**81503-AAA/GJG/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8088	FILED BY	Andrew Gorman
PATENT CENTER #	68755898	AUTHORIZED BY	-
CUSTOMER #	23432	FILING DATE	02/07/2019
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	James Hicks

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 1044	**E20251EG02465004**	**Andrew Gorman**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL AMOUNT:	**$480.00**

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 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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

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CUSTOMER #	23432	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
250115_81503-AAA_IssueFee_AD.pdf	1	Issue Fee Payment (PTO-85B)	113 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
250115_81503-AAA_IssueFee_AD.pdf	35F5A01A946B36CC82ED2D218E254D9D1F3D185EB2D87B71302ACCBD19F2360BF214DD8CC077E6345B7989DBE3DCE17FE6D352312252A9353946DD761C9AB53E

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PART B - FEE(S) TRANSMITTAL

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

By fax, send to: (571)-273-2885

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23432 7590 01/13/2025

Gary J. Gershik; John P. White; Paul Teng
AMSTER ROTHSTEIN & EBENSTEIN LLP
405 Lexington Avenue, 48th Floor
New York, NY 10174

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

TITLE OF INVENTION: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	04/14/2025

EXAMINER	ART UNIT	CLASS-SUBCLASS
LU, FRANK WEI MIN	1683	435-006110

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Gary J. Gershik
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: COLD SPRING HARBOR LABORATORY

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Cold Spring Harbor, New York

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ■ Corporation or other private group entity ❑ Government

4a. Fees submitted: ■ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

■ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Gary J. Gershik/ Date January 15, 2025

Typed or printed name Gary J. Gershik Registration No. 39,992

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 5981/81503-AAA/GJG/ADR	Application No. 16/269,818
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		First Named Inventor James Hicks	Confirmation Number 8088
		Filing Date February 7, 2019	Group Art Unit Not yet assigned

Change(s) applied to document, /M.E.G./ 1/14/2025

U.S. Patent Documents

Examiner Initial	Cite ID[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM/DD/YYYY	First named inventor
	1	9,670,536 06/2017	~~6/6/2018~~	Casbon
	2	9,487,829	11/8/2016	Vogelstein
	3	9,476,095	10/25/2016	Vogelstein
	4	9,404,156	8/2/2016	Hicks
	5	8,741,606	6/3/2014	Casbon
	6	8,694,263	4/8/2014	Wigler
	7	8,663,917	3/4/2014	Wigler
	8	8,554,488	10/8/2013	Wigler
	9	8,273,871	9/25/2012	Hannon
	10	7,700,324	4/20/2010	Issa
	11	7,622,281	11/24/2009	Ronaghi
	12	7,537,897	5/26/2009	Brenner
	13	7,531,307	5/12/2009	Wigler
	14	6,569,617	5/27/2003	Wigler
	15	6,172,214	1/9/2001	Brenner
	16	6,013,445	1/11/2000	Albrecht
	17	5,639,603	6/17/1997	Dower
	18	2017/0051347 A1	2/23/2017	Vogelstein
	19	2016/0251715 A1	9/1/2016	Hicks
	20	2016/0215333 A1	7/28/2016	Vogelstein
	21	2014/0025307	1/23/2014	Wigler
	22	2013/0179999	7/11/2013	Hannon
	23	2012/0328607	12/27/2012	Hicks
	24	2012/0149593	6/14/2012	Hicks
	25	2010/0227768	9/10/2010	Wigler
	26	2010/0203538	8/12/2010	Dube

Examiner Signature	Date Considered
/FRANK W LU/	03/26/2021

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Substitute Disclosure Form (PTO-1449)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /F.W.L/

FIRST IDS EXHIBIT A

IPR2025-01353 CSHL EX2001

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United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/25/2025	12234510	81503-AAA/GJG/ADR	8088

23432 7590 02/05/2025

Gary J. Gershik; John P. White; Paul Teng
AMSTER ROTHSTEIN & EBENSTEIN LLP
405 Lexington Avenue, 48th Floor
New York, NY 10174

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

James Hicks, Locust Valley, NY;
Nicholas Navin, Houston, TX;
Jennifer Troge, Oyster Bay, NY;
Zihua Wang, Huntington, NY;
Michael Wigler, Cold Spring Harbor, NY;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Cold Spring Harbor Laboratory, Cold Spring Harbor, NY;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Placeholder Sheet for Supplemental Content

Application Number: 16269818 Document Date: 02/25/2025

The presence of this form indicates that the following document type was received in electronic format on the date identified above. This document is stored separately from the typical case contents which are stored in image format.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded and no paper documents or physical media exist.

- Patent Grant with Color/Grayscale Drawings

At the time of document entry (noted above):

- USPTO employees may access this supplemental content via Docket Application Viewer (DAV) or Supplemental Content Viewer (SCV).
- External customers may access this supplemental content via Patent Center.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 02/25/2025

Gary J. Gershik; John P. White; Paul Teng
AMSTER ROTHSTEIN & EBENSTEIN LLP
405 Lexington Avenue, 48th Floor
New York, NY 10174

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1683	

NOTIFICATION DATE	DELIVERY MODE
02/25/2025	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):

PTODOCKET@ARELAW.COM
klees@ARELAW.com
patcomm-in-grp@cooperdunham.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
16/269,818	25-Feb-2025	12234510

Gary J. Gershik; John P. White; Paul Teng
AMSTER ROTHSTEIN & EBENSTEIN LLP
405 Lexington Avenue, 48th Floor
New York, NY 10174

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants

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ACKNOWLEDGEMENT OF LOSS OF ENTITLEMENT TO ENTITY STATUS DISCOUNT

APPLICATION #	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET #	REQUEST ID
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	400363

The entity status change request below filed through Patent Center on 05/07/2025 has been accepted.

Certifications

APPLICANT CHANGING TO REGULAR UNDISCOUNTED FEE STATUS

Signature

I certify, in accordance with 37 CFR 1.4(d)(4), that I am one of the signatories making the entity status change.

Signature	Name	Registration #
/Gary J. Gershik/	Gary Gershik	39992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee(s) : Cold Spring Harbor Laboratory

U.S. Patent No. : 12,234,510

Issue Date : February 25, 2025

U.S. Serial No. : 16/269,818 Examiner : Frank Lu

Filing Date : February 7, 2019 Art Unit : 1683

Confirmation No. : 8088

For : VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

405 Lexington Avenue, 48th Fl
New York, NY 10174
May 7, 2025

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

PETITION UNDER 37 C.F.R. §1.28(c) TO CORRECT PAYMENT OF ISSUE FEE PAID AT SMALL ENTITY RATE

The Patentee hereby petitions to correct payment of the issue fee unintentionally paid on January 15, 2025 at the small entity rate.

On January 15, 2025, the issue fee was paid in error at the small entity rate in connection with the application that issued as the subject patent. Subsequently, the undersigned discovered that the entitlement to small entity status was lost by January 15, 2025 in connection with the application that issued as the subject patent.

37 C.F.R. §1.28(c) provides that errors in small entity status will be excused upon compliance with its provisions as follows:

> "[i]f status as a small entity is established in good faith, and fees as a small entity are paid in good faith, in any application or patent, and ... that through error the Office was not notified of a loss of entitlement to small entity status as required by § 1.27(g)(2), the error will be excused upon: compliance with the separate submission and itemization requirements of paragraphs (c)(1) and (c)(2) of this section, and the deficiency payment requirement of paragraph (c)(2) of this section"

Small entity status was correctly established upon the filing of U.S. Application No. 16/269,818, which issued as the subject patent. Thus, "small entity status was established in good faith" in connection with the application that issued as the subject patent, as required by 37 C.F.R. §1.28(c). On January 15, 2025, the issue fee was paid in good faith at the small entity rate. Subsequently, the undersigned discovered that the entitlement to small entity status was lost in 2024 when Applicant licensed the subject matter of the subject patent to non-small entity. Through error, the U.S. Patent Office was "not notified of a loss of entitlement to small entity status as required by 37 C.F.R. 1.27(g)(2)" by the time the issue fee was paid on January 15, 2025.

In view of the foregoing, 37 C.F.R. §1.28(c) provides that the error will be excused upon compliance with the separate submission requirement of paragraph (c)(1), the itemization requirements of paragraph (c)(2) and the deficiency payment requirement of paragraph (c)(2).

The filing of this Petition in connection with U.S. Patent No. 12,234,510 satisfies the separate submission requirement of 37 C.F.R. §1.28(c)(1).

The itemization below along with the payment authorization submitted herewith satisfy the requirements of 37 C.F.R. §1.28(c)(2).

Particular Type of Fee Erroneously Paid	**Current Fee at Large Entity Rate**	**Small Entity Amount Actually Paid**	**Date Small Entity Amount Paid**	**Amount of Fee Deficiency Owed**
Issue Fee	$ 1,290.00	$ 480.00	January 15, 2025	$810.00
Total				**$810.00**

Pursuant to 37 C.F.R. §1.28(c)(2), Patentee hereby supplements the Issue Fee paid on January 15, 2025 with the deficiency of EIGHT HUNDRED TEN DOLLARS ($810.00). Authorization is hereby given to charge the amount of $810.00 to Deposit Account No. 01-1785.

Finally, pursuant to 37 C.F.R. §1.28(d), Patentee understands that the payment of the deficiency will be treated by the U.S. Patent Office as a notification of loss of small entity status in connection with the subject patent. Furthermore, Patentee is updating the U.S. Patent Office records for the subject patent to reflect that future fees shall be paid at the large entity rate.

No fee, other than the enclosed $810.00 fee is deemed necessary in connection with the filing of this Petition. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

/Gary J. Gershik/

_____

Gary J. Gershik
Registration No. 39,992
Amster Rothstein & Ebenstein LLP
405 Lexington Avenue
48th Floor
New York, NY 10174
(212) 336-8000

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on May 7, 2025.

/Darren Haber/

_____
Darren Haber
Registration No. 80,964

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
16/269,818	**05/07/2025 02:57:26 PM Z ET**	**81503-AAA/GJG/ADR**

Title of Invention

VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	12234510
CONFIRMATION #	8088	FILED BY	Darren Haber
PATENT CENTER #	70330117	FILING DATE	02/07/2019
CUSTOMER #	23432	FIRST NAMED INVENTOR	James Hicks
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Gary Gershik

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
202050507_81503-AAA_IssueFeePetition_DH.pdf	3	Notification of loss of entitlement to small entity status	129 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
202050507_81503-AAA_IssueFeePetition_DH.pdf	696ED1DBDFE706E00F8BEC0092FB96492B8E5FF9D9E7A2D33A66D4FE05D76DD3DFDF78BEBF82466DDBB0D77C08B2276E3F06C6F53CF69DD018090B21755EAF25

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

IPR2025-01353
CSHL EX2001

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.

Document Code:WFEE

User :Chhivindavy Khlok

Sale Accounting Date:06/02/2025

Sale Item Reference Number	Effective Date
16269818	05/07/2025

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I202562046398017	1461	1.28(C) SUBMISSIONS - APPLIC FILE FEE	$810.00	Deposit Account

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/269,818	02/07/2019	James Hicks	81503-AAA/GJG/ADR	8088

23432 7590 06/04/2025

Gary J. Gershik; John P. White; Paul Teng
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405 Lexington Avenue, 48th Floor
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EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1683	

NOTIFICATION DATE	DELIVERY MODE
06/04/2025	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):

PTODOCKET@ARELAW.COM
klees@ARELAW.com
patcomm-in-grp@cooperdunham.com

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Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
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In re Patent No. 12,234,510	:	
Issue Date: May 9, 2024	:	
Application No. 16/269,818	:	
Filed: February 7, 2019	:	DECISION ON PETITION
For: VARIETAL COUNTING OF NUCLEIC ACIDS FOR OBTAINING GENOMIC COPY NUMBER INFORMATION	:	

This is a Notice regarding the request for acceptance of a fee deficiency submission under 37 CFR 1.28(c) filed May 7, 2025.

There is no indication that the request is signed by a registered patent attorney or patent agent of record. However, in accordance with 37 CFR 1.34, the signature of Gary J. Gershik appearing on the correspondence shall constitute a representation to the United States Patent and Trademark Office that he or she is authorized to represent the particular party on whose behalf he or she acts.

The fee deficiency submission under 37 CFR 1.28(c) is **ACCEPTED**. Accordingly, status as a small entity has been removed and any future fee(s) submitted must be paid at the undiscounted rate.

Inquiries related to this communication should be directed to Ann Marie Ziegler at (571) 272-7151.

/ANN MARIE ZIEGLER/
Ann Marie Ziegler
Paralegal Specialist, Office of Petitions