8501621

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 26, 2024

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: ***16/575,128***
FILING DATE: ***September 18, 2019***
PATENT NUMBER: ***10793916***
ISSUE DATE: ***October 06, 2020***

Certified by

Katherine Kelly Vidal

Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

PTO/AIA/15 (10-17)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	42534-704.313
First Named Inventor	AmirAli TALASAZ
Title	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER V
Priority Mail Express® Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [✔] **Fee Transmittal Form** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [✔] **Specification** [*Total Pages* 84] Both the claims and abstract must start on a new page. *(See MPEP § 608.01(a) for information on the preferred arrangement)*
5. [✔] **Drawing(s)** (35 U.S.C. 113) [*Total Sheets* 16]
6. **Inventor's Oath or Declaration** [*Total Pages* 1] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. [ ] Newly executed (original or copy)
   b. [✔] A copy from a prior application (37 CFR 1.63(d))
7. [✔] **Application Data Sheet** ** See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. **CD-ROM or CD-R** in duplicate, large table, or Computer Program (*Appendix*)
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** (*if applicable, items a. – c. are required*)
   a. [ ] Computer Readable Form (CRF)
   b. [ ] Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or
      ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO:

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

ACCOMPANYING APPLICATION PAPERS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee _____
11. [✔] **37 CFR 3.73(c) Statement** (*when there is an assignee*) [✔] **Power of Attorney**
12. [ ] **English Translation Document** (*if applicable*)
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [ ] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** (*MPEP § 503*) (*Should be specifically itemized*)
16. [ ] **Certified Copy of Priority Document(s)** (*if foreign priority is claimed*)
17. [ ] **Nonpublication Request** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [✔] **Other:** Track One Request

Note*: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS

[✘] The address associated with Customer Number: 115823 **OR** [ ] Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/Timothy A. Hott/	Date	2019-09-18
Name (Print/Type)	Timothy A. Hott	Registration No. (Attorney/Agent)	67740

This collection of information is required by 37 CFR 1.53(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.

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-704.313
	Application Number	
Title of Invention	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION	

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
	AmirAli		TALASAZ	

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

City	Atherton	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	505 Penobscot Drive		
Address 2			
City	Redwood City	**State/Province**	CA
Postal Code	94063	**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.**

Customer Number	115823		
Email Address	patents@guardanthealth.com	Add Email	Remove Email
Email Address	patentdocket@wsgr.com	Add Email	Remove Email

Application Information:

Title of the Invention	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION		
Attorney Docket Number	42534-704.313	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	16	**Suggested Figure for Publication (if any)**	

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	Application Number	
Title of Invention	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION	

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	115823		

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	16283635	2019-02-22

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	Application Number	
Title of Invention	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION	

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16283635	Continuation of	15872831	2018-01-16
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15872831	Continuation of	15828099	2017-11-30
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15828099	Continuation of	15467570	2017-03-23	9840743	2017-12-12

Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15467570	Continuation of	14425189	2015-03-02	10041127	2018-08-07

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14425189	a 371 of international	PCTUS1358061	2013-09-04
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS1358061	Claims benefit of provisional	61845987	2013-07-13
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS1358061	Claims benefit of provisional	61793997	2013-03-15
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS1358061	Claims benefit of provisional	61704400	2012-09-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCTUS1358061	Claims benefit of provisional	61696734	2012-09-04

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

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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

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

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-704.313
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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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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-704.313
	Application Number	
Title of Invention	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION	

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	GUARDANT HEALTH, INC.		
Mailing Address Information For Applicant:			
Address 1	505 Penobscot Drive		
Address 2			
City	Redwood City	**State/Province**	CA
Country	US	Postal Code	94063
Phone Number		Fax Number	
Email Address	patents@guardanthealth.com		

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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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-704.313
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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. ☐

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

Mailing Address Information For Assignee including Non-Applicant Assignee:

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

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

Remove

Signature:

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

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

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

Signature	/Timothy A. Hott/			Date (YYYY-MM-DD)	2019-09-18
First Name	Timothy	Last Name	Hott	Registration Number	67740

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	42534-704.313
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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 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.

SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Patent Application No. 16/283,635, filed February 22, 2019, which is a continuation of U.S. Patent Application No. 15/872,831, filed January 16, 2018, which is a continuation application of U.S. Patent Application No. 15/828,099, filed November 30, 2017, which is a continuation application of U.S. Patent Application No. 15/467,570, filed March 23, 2017 (now U.S. Patent 9,840,743, issued December 12, 2017), which is a continuation application of U.S. Patent Application No. 14/425,189, filed March 2, 2015, (now U.S. Patent 10,041,127, issued August 7, 2018) which is a national stage entry of international Application No. PCT/US2013/058061, filed September 4, 2013, which claims priority to U.S. Provisional Patent Application No. 61/696,734, filed September 4, 2012, U.S. Provisional Patent Application No. 61/704,400, filed September 21, 2012, and U.S. Provisional Patent Application No. 61/793,997, filed March 15, 2013, and U.S. Provisional Patent Application No. 61/845,987, filed July 13, 2013, each of which is entirely incorporated herein by reference for all purposes.

BACKGROUND OF THE INVENTION

[0002] The detection and quantification of polynucleotides is important for molecular biology and medical applications such as diagnostics. Genetic testing is particularly useful for a number of diagnostic methods. For example, disorders that are caused by rare genetic alterations (e.g., sequence variants) or changes in epigenetic markers, such as cancer and partial or complete aneuploidy, may be detected or more accurately characterized with DNA sequence information.

[0003] Early detection and monitoring of genetic diseases, such as cancer is often useful and needed in the successful treatment or management of the disease. One approach may include the monitoring of a sample derived from cell free nucleic acids, a population of polynucleotides that can be found in different types of bodily fluids. In some cases, disease may be characterized or detected based on detection of genetic aberrations, such as a change in copy number variation and/or sequence variation of one or more nucleic acid sequences, or the development of other certain rare genetic alterations. Cell free DNA ("cfDNA") has been known in the art for decades, and may contain genetic aberrations associated with a particular disease. With improvements in sequencing and techniques to manipulate nucleic acids, there is a need in the art for improved methods and systems for using cell free DNA to detect and monitor disease.

SUMMARY OF THE INVENTION

[0004] The disclosure provides for a method for detecting copy number variation comprising: a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide are optionally attached to unique barcodes; b) filtering out reads that fail to meet a set threshold; c) mapping sequence reads obtained from step (a) to a reference sequence; d) quantifying/counting mapped reads in two or more predefined regions of the reference sequence; e) determining a copy number variation in one or more of the predefined regions by (i) normalizing the number of reads in the predefined regions to each other and/or the number of unique barcodes in the predefined regions to each other; and (ii) comparing the normalized numbers obtained in step (i) to normalized numbers obtained from a control sample.

[0005] The disclosure also provides for a method for detecting a rare mutation in a cell-free or substantially cell free sample obtained from a subject comprising: a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide generate a plurality of sequencing reads; b) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide generate a plurality of sequencing reads; sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide generate a plurality of sequencing reads; c) filtering out reads that fail to meet a set threshold; d) mapping sequence reads derived from the sequencing onto a reference sequence; e) identifying a subset of mapped sequence reads that align with a variant of the reference sequence at each mappable base position; f) for each mappable base position, calculating a ratio of (a) a number of mapped sequence reads that include a variant as compared to the reference sequence, to (b) a number of total sequence reads for each mappable base position; g) normalizing the ratios or frequency of variance for each mappable base position and determining potential rare variant(s) or mutation(s); h) and comparing the resulting number for each of the regions with potential rare variant(s) or mutation(s) to similarly derived numbers from a reference sample.

[0006] Additionally, the disclosure also provides for a method of characterizing the heterogeneity of an abnormal condition in a subject, the method comprising generating a genetic profile of extracellular polynucleotides in the subject, wherein the genetic profile comprises a plurality of data resulting from copy number variation and/or other rare mutation (e.g., genetic alteration) analyses.

[0007] In some embodiments, the prevalence/concentration of each rare variant identified in the subject is reported and quantified simultaneously. In other embodiments, a confidence score, regarding the prevalence/concentrations of rare variants in the subject, is reported.

[0008] In some embodiments, extracellular polynucleotides comprise DNA. In other embodiments, extracellular polynucleotides comprise RNA. Polynucleotides may be fragments or fragmented after isolation. Additionally, the disclosure provides for a method for circulating nucleic acid isolation and extraction.

[0009] In some embodiments, extracellular polynucleotides are isolated from a bodily sample that may be selected from a group consisting of blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool and tears.

[0010] In some embodiments, the methods of the disclosure also comprise a step of determining the percent of sequences having copy number variation or other rare genetic alteration (e.g., sequence variants) in said bodily sample.

[0011] In some embodiments, the percent of sequences having copy number variation in said bodily sample is determined by calculating the percentage of predefined regions with an amount of polynucleotides above or below a predetermined threshold.

[0012] In some embodiments, bodily fluids are drawn from a subject suspected of having an abnormal condition which may be selected from the group consisting of, mutations, rare mutations, single nucleotide variants, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection and cancer.

[0013] In some embodiments, the subject may be a pregnant female in which the abnormal condition may be a fetal abnormality selected from the group consisting of, single nucleotide variants, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection and cancer

[0014] In some embodiments, the method may comprise comprising attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to sequencing, in which the barcodes comprise are unique. In other embodiments barcodes attached to extracellular polynucleotides or fragments thereof prior to sequencing are not unique.

[0015] In some embodiments, the methods of the disclosure may comprise selectively enriching regions from the subject's genome or transcriptome prior to sequencing. In other embodiments the methods of the disclosure comprise selectively enriching regions from the subject's genome or transcriptome prior to sequencing. In other embodiments the methods of the disclosure comprise non-selectively enriching regions from the subject's genome or transcriptome prior to sequencing.

[0016] Further, the methods of the disclosure comprise attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to any amplification or enrichment step.

[0017] In some embodiments, the barcode is a polynucleotide, which may further comprise random sequence or a fixed or semi-random set of oligonucleotides that in combination with the diversity of molecules sequenced from a select region enables identification of unique molecules and be at least a 3, 5, 10, 15, 20 25, 30, 35, 40, 45, or 50mer base pairs in length.

[0018] In some embodiments, extracellular polynucleotides or fragments thereof may be amplified. In some embodiments amplification comprises global amplification or whole genome amplification.

[0019] In some embodiments, sequence reads of unique identity may be detected based on sequence information at the beginning (start) and end (stop) regions of the sequence read and the length of the sequence read. In other embodiments sequence molecules of unique identity are detected based on sequence information at the beginning (start) and end (stop) regions of the sequence read, the length of the sequence read and attachment of a barcode.

[0020] In some embodiments, amplification comprises selective amplification, non-selective amplification, suppression amplification or subtractive enrichment.

[0021] In some embodiments, the methods of the disclosure comprise removing a subset of the reads from further analysis prior to quantifying or enumerating reads.

[0022] In some embodiments, the method may comprise filtering out reads with an accuracy or quality score of less than a threshold, e.g., 90%, 99%, 99.9%, or 99.99% and/or mapping score less than a threshold, e.g., 90%, 99%, 99.9% or 99.99%. In other embodiments, methods of the disclosure comprise filtering reads with a quality score lower than a set threshold.

[0023] In some embodiments, predefined regions are uniform or substantially uniform in size, about 10kb, 20kb, 30kb 40kb, 50kb, 60kb, 70kb, 80kb, 90kb, or 100kb in size. In some embodiments, at least 50, 100, 200, 500, 1000, 2000, 5000, 10,000, 20,000, or 50,000 regions are analyzed.

[0024] In some embodiments, a genetic variant, rare mutation or copy number variation occurs in a region of the genome selected from the group consisting of gene fusions, gene duplications, gene deletions, gene translocations, microsatellite regions, gene fragments or combination thereof. In other embodiments a genetic variant, rare mutation, or copy number variation occurs in a region of the genome selected from the group consisting of genes, oncogenes, tumor suppressor genes, promoters, regulatory sequence elements, or combination thereof. In some embodiments the variant is a nucleotide variant, single base substitution, or small indel, transversion, translocation, inversion, deletion, truncation or gene truncation about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15 or 20 nucleotides in length.

[0025] In some embodiments, the method comprises correcting/normalizing/adjusting the quantity of mapped reads using the barcodes or unique properties of individual reads.

[0026] In some embodiments, enumerating the reads is performed through enumeration of unique barcodes in each of the predefined regions and normalizing those numbers across at least a subset of predefined regions that were sequenced. In some embodiments, samples at succeeding time intervals from the same subject are analyzed and compared to previous sample results. The method of the disclosure may further comprise determining partial copy number variation frequency, loss of heterozygosity, gene expression analysis, epigenetic analysis and hypermethylation analysis after amplifying the barcode-attached extracellular polynucleotides.

[0027] In some embodiments, copy number variation and rare mutation analysis is determined in a cell-free or substantially cell free sample obtained from a subject using multiplex sequencing, comprising performing over 10,000 sequencing reactions; simultaneously sequencing at least 10,000 different reads; or performing data analysis on at least 10,000 different reads across the genome. The method may comprise multiplex sequencing comprising performing data analysis on at least 10,000 different reads across the genome. The method may further comprise enumerating sequenced reads that are uniquely identifiable.

[0028] In some embodiments, the methods of the disclosure comprise normalizing and detection is performed using one or more of hidden markov, dynamic programming, support vector machine, Bayesian network, trellis decoding, Viterbi decoding, expectation maximization, Kalman filtering, or neural network methodologies.

[0029] In some embodiments the methods of the disclosure comprise monitoring disease progression, monitoring residual disease, monitoring therapy, diagnosing a condition, prognosing a condition, or selecting a therapy based on discovered variants.

[0030] In some embodiments, a therapy is modified based on the most recent sample analysis. Further, the methods of the disclosure comprise inferring the genetic profile of a tumor, infection or other tissue abnormality. In some embodiments growth, remission or evolution of a tumor, infection or other tissue abnormality is monitored. In some embodiments the subject's immune system are analyzed and monitored at single instances or over time.

[0031] In some embodiments, the methods of the disclosure comprise identification of a variant that is followed up through an imaging test (e.g., CT, PET-CT, MRI, X-ray, ultrasound) for localization of the tissue abnormality suspected of causing the identified variant.

[0032] In some embodiments, the methods of the disclosure comprise use of genetic data obtained from a tissue or tumor biopsy from the same patient. In some embodiments, whereby the phylogenetics of a tumor, infection or other tissue abnormality is inferred.

[0033] In some embodiments, the methods of the disclosure comprise performing population-based no-calling and identification of low-confidence regions. In some embodiments, obtaining the measurement data for the sequence coverage comprises measuring sequence coverage depth at every position of the genome. In some embodiments correcting the measurement data for the sequence coverage bias comprises calculating window-averaged coverage. In some embodiments correcting the measurement data for the sequence coverage bias comprises performing adjustments to account for GC bias in the library construction and sequencing process. In some embodiments correcting the measurement data for the sequence coverage bias comprises performing adjustments based on additional weighting factor associated with individual mappings to compensate for bias.

[0034] In some embodiments, the methods of the disclosure comprise extracellular polynucleotide derived from a diseased cell origin. In some embodiments, the extracellular polynucleotide is derived from a healthy cell origin.

[0035] The disclosure also provides for a system comprising a computer readable medium for performing the following steps: selecting predefined regions in a genome; enumerating number of sequence reads in the predefined regions; normalizing the number of sequence reads across the predefined regions; and determining percent of copy number variation in the predefined regions. In some embodiments, the entirety of the genome or at least 10%, 20%, 30%, 40%, 50%, 60%, 70%,

80%, or 90% of the genome is analyzed. In some embodiments, computer readable medium provides data on percent cancer DNA or RNA in plasma or serum to the end user.

[0036] In some embodiments, the amount of genetic variation, such as polymorphisms or causal variants is analyzed. In some embodiments, the presence or absence of genetic alterations is detected.

[0037] The disclosure also provides for a method for detecting a rare mutation in a cell-free or a substantially cell free sample obtained from a subject comprising: a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generate a plurality of sequencing reads; b) filtering out reads that fail to meet a set threshold; c) mapping sequence reads derived from the sequencing onto a reference sequence; d) identifying a subset of mapped sequence reads that align with a variant of the reference sequence at each mappable base position; e) for each mappable base position, calculating a ratio of (a) a number of mapped sequence reads that include a variant as compared to the reference sequence, to (b) a number of total sequence reads for each mappable base position; f) normalizing the ratios or frequency of variance for each mappable base position and determining potential rare variant(s) or other genetic alteration(s); and g) comparing the resulting number for each of the regions

[0038] This disclosure also provides for a method comprising: a. providing at least one set of tagged parent polynucleotides, and for each set of tagged parent polynucleotides; b. amplifying the tagged parent polynucleotides in the set to produce a corresponding set of amplified progeny polynucleotides; c. sequencing a subset (including a proper subset) of the set of amplified progeny polynucleotides, to produce a set of sequencing reads; and d. collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides. In certain embodiments the method further comprises: e. analyzing the set of consensus sequences for each set of tagged parent molecules.

[0039] In some embodiments each polynucleotide in a set is mappable to a reference sequence.

[0040] In some embodiments the method comprises providing a plurality of sets of tagged parent polynucleotides, wherein each set is mappable to a different reference sequence.

[0041] In some embodiments the method further comprises converting initial starting genetic material into the tagged parent polynucleotides.

[0042] In some embodiments the initial starting genetic material comprises no more than 100 ng of polynucleotides.

[0043] In some embodiments the method comprises bottlenecking the initial starting genetic material prior to converting.

[0044] In some embodiments the method comprises converting the initial starting genetic material into tagged parent polynucleotides with a conversion efficiency of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 80% or at least 90%.

[0045] In some embodiments converting comprises any of blunt-end ligation, sticky end ligation, molecular inversion probes, PCR, ligation-based PCR, single strand ligation and single strand circularization.

[0046] In some embodiments the initial starting genetic material is cell-free nucleic acid.

[0047] In some embodiments a plurality of the reference sequences are from the same genome.

[0048] In some embodiments each tagged parent polynucleotide in the set is uniquely tagged.

[0049] In some embodiments the tags are non-unique.

[0050] In some embodiments the generation of consensus sequences is based on information from the tag and/or at least one of sequence information at the beginning (start) region of the sequence read, the end (stop) regions of the sequence read and the length of the sequence read.

[0051] In some embodiments the method comprises sequencing a subset of the set of amplified progeny polynucleotides sufficient to produce sequence reads for at least one progeny from of each of at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% at least 95%, at least 98%, at least 99%, at least 99.9% or at least 99.99% of unique polynucleotides in the set of tagged parent polynucleotides.

[0052] In some embodiments the at least one progeny is a plurality of progeny, e.g., at least 2, at least 5 or at least 10 progeny.

[0053] In some embodiments the number of sequence reads in the set of sequence reads is greater than the number of unique tagged parent polynucleotides in the set of tagged parent polynucleotides.

[0054] In some embodiments the subset of the set of amplified progeny polynucleotides sequenced is of sufficient size so that any nucleotide sequence represented in the set of tagged parent polynucleotides at a percentage that is the same as the percentage per-base sequencing error rate of the sequencing platform used, has at least a 50%, at least a 60%, at least a 70%, at least a 80%, at least a 90% at least a 95%, at least a 98%, at least a 99%, at least a 99.9% or at least a 99.99% chance of being represented among the set of consensus sequences.

[0055] In some embodiments the method comprises enriching the set of amplified progeny polynucleotides for polynucleotides mapping to one or more selected reference sequences by: (i)

selective amplification of sequences from initial starting genetic material converted to tagged parent polynucleotides; (ii) selective amplification of tagged parent polynucleotides; (iii) selective sequence capture of amplified progeny polynucleotides; or (iv) selective sequence capture of initial starting genetic material.

[0056] In some embodiments analyzing comprises normalizing a measure (e.g., number) taken from a set of consensus sequences against a measure taken from a set of consensus sequences from a control sample.

[0057] In some embodiments analyzing comprises detecting mutations, rare mutations, single nucleotide variants, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection or cancer.

[0058] In some embodiments the polynucleotides comprise DNA, RNA, a combination of the two or DNA plus RNA-derived cDNA.

[0059] In some embodiments a certain subset of polynucleotides is selected for or is enriched based on polynucleotide length in base-pairs from the initial set of polynucleotides or from the amplified polynucleotides.

[0060] In some embodiments analysis further comprises detection and monitoring of an abnormality or disease within an individual, such as, infection and/or cancer.

[0061] In some embodiments the method is performed in combination with immune repertoire profiling.

[0062] In some embodiments the polynucleotides are extract from the group consisting of blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool, and tears.

[0063] In some embodiments collapsing comprising detecting and/or correcting errors, nicks or lesions present in the sense or anti-sense strand of the tagged parent polynucleotides or amplified progeny polynucleotides.

[0064] This disclosure also provides for a method comprising detecting genetic variation in initial starting genetic material with a sensitivity of at least 5%, at least 1%, at least 0.5%, at least 0.1% or at least 0.05%. In some embodiments the initial starting genetic material is provided in an amount less than 100 ng of nucleic acid, the genetic variation is copy number/heterozygosity variation and

detecting is performed with sub-chromosomal resolution; e.g., at least 100 megabase resolution, at least 10 megabase resolution, at least 1 megabase resolution, at least 100 kilobase resolution, at least 10 kilobase resolution or at least 1 kilobase resolution. In another embodiment the method comprises providing a plurality of sets of tagged parent polynucleotides, wherein each set is mappable to a different reference sequence. In another embodiment the reference sequence is the locus of a tumor marker, and analyzing comprises detecting the tumor marker in the set of consensus sequences. In another embodiment the tumor marker is present in the set of consensus sequences at a frequency less than the error rate introduced at the amplifying step. In another embodiment the at least one set is a plurality of sets, and the reference sequences comprise a plurality of reference sequences, each of which is the locus of a tumor marker. In another embodiment analyzing comprises detecting copy number variation of consensus sequences between at least two sets of parent polynucleotides. In another embodiment analyzing comprises detecting the presence of sequence variations compared with the reference sequences. In another embodiment analyzing comprises detecting the presence of sequence variations compared with the reference sequences and detecting copy number variation of consensus sequences between at least two sets of parent polynucleotides. In another embodiment collapsing comprises: i. grouping sequences reads sequenced from amplified progeny polynucleotides into families, each family amplified from the same tagged parent polynucleotide; and ii. determining a consensus sequence based on sequence reads in a family.

[0065] This disclosure also provides for a system comprising a computer readable medium for performing the following steps: a. providing at least one set of tagged parent polynucleotides, and for each set of tagged parent polynucleotides; b. amplifying the tagged parent polynucleotides in the set to produce a corresponding set of amplified progeny polynucleotides; c. sequencing a subset (including a proper subset) of the set of amplified progeny polynucleotides, to produce a set of sequencing reads; and d. collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides and, optionally, e. analyzing the set of consensus sequences for each set of tagged parent molecules.

[0066] This disclosure also provides a method comprising: a. providing at least one set of tagged parent polynucleotides, and for each set of tagged parent polynucleotides; b. amplifying the tagged parent polynucleotides in the set to produce a corresponding set of amplified progeny polynucleotides; c. sequencing a subset (including a proper subset) of the set of amplified progeny polynucleotides, to produce a set of sequencing reads; d. collapsing the set of sequencing reads to

generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides; and e. filtering out from among the consensus sequences those that fail to meet a quality threshold. In one embodiment the quality threshold considers a number of sequence reads from amplified progeny polynucleotides collapsed into a consensus sequence. In another embodiment the quality threshold considers a number of sequence reads from amplified progeny polynucleotides collapsed into a consensus sequence. This disclosure also provides a system comprising a computer readable medium for performing the aforesaid method.

[0067] This disclosure also provides a method comprising: a. providing at least one set of tagged parent polynucleotides, wherein each set maps to a different reference sequence in one or more genomes, and, for each set of tagged parent polynucleotides; i. amplifying the first polynucleotides to produce a set of amplified polynucleotides; ii. sequencing a subset of the set of amplified polynucleotides, to produce a set of sequencing reads; and iii. collapsing the sequence reads by: 1. grouping sequences reads sequenced from amplified progeny polynucleotides into families, each family amplified from the same tagged parent polynucleotide. In one embodiment collapsing further comprises: 2. determining a quantitative measure of sequence reads in each family. In another embodiment the method further comprises (including a) including a): b. determining a quantitative measure of unique families; and c. based on (1) the quantitative measure of unique families and (2) the quantitative measure of sequence reads in each group, inferring a measure of unique tagged parent polynucleotides in the set. In another embodiment inferring is performed using statistical or probabilistic models. In another embodiment wherein the at least one set is a plurality of sets. In another embodiment the method further comprises correcting for amplification or representational bias between the two sets. In another embodiment the method further comprises using a control or set of control samples to correct for amplification or representational biases between the two sets. In another embodiment the method further comprises determining copy number variation between the sets. In another embodiment the method further comprises (including a, b, c): d. determining a quantitative measure of polymorphic forms among the families; and e. based on the determined quantitative measure of polymorphic forms, inferring a quantitative measure of polymorphic forms in the number of inferred unique tagged parent polynucleotides. In another embodiment wherein polymorphic forms include but are not limited to: substitutions, insertions, deletions, inversions, microsatellite changes, transversions, translocations, fusions, methylation, hypermethylation, hyrdroxymethylation, acetylation, epigenetic variants, regulatory-associated variants or protein

binding sites. In another embodiment wherein the sets derive from a common sample, the method further comprising: a. inferring copy number variation for the plurality of sets based on a comparison of the inferred number of tagged parent polynucleotides in each set mapping to each of a plurality of reference sequences. In another embodiment the original number of polynucleotides in each set is further inferred. This disclosure also provides a system comprising a computer readable medium for performing the aforesaid methods.

[0068] This disclosure also provides a method of determining copy number variation in a sample that includes polynucleotides, the method comprising: a. providing at least two sets of first polynucleotides, wherein each set maps to a different reference sequence in a genome, and, for each set of first polynucleotides; i. amplifying the polynucleotides to produce a set of amplified polynucleotides; ii. sequencing a subset of the set of amplified polynucleotides, to produce a set of sequencing reads; iii. grouping sequences reads sequenced from amplified polynucleotides into families, each family amplified from the same first polynucleotide in the set; iv. inferring a quantitative measure of families in the set; b. determining copy number variation by comparing the quantitative measure of families in each set. This disclosure also provides a system comprising a computer readable medium for performing the aforesaid methods.

[0069] This disclosure also provides a method of inferring frequency of sequence calls in a sample of polynucleotides comprising: a. providing at least one set of first polynucleotides, wherein each set maps to a different reference sequence in one or more genomes, and, for each set of first polynucleotides; i. amplifying the first polynucleotides to produce a set of amplified polynucleotides; ii. sequencing a subset of the set of amplified polynucleotides, to produce a set of sequencing reads; iii. grouping the sequence reads into families, each family comprising sequence reads of amplified polynucleotides amplified from the same first polynucleotide; b. inferring, for each set of first polynucleotides, a call frequency for one or more bases in the set of first polynucleotides, wherein inferring comprises: i. assigning, for each family, confidence score for each of a plurality of calls, the confidence score taking into consideration a frequency of the call among members of the family; and ii. estimating a frequency of the one or more calls taking into consideration the confidence scores of the one or more calls assigned to each family. This disclosure also provides a system comprising a computer readable medium for performing the aforesaid methods.

[0070] This disclosure also provides a method of communicating sequence information about at least one individual polynucleotide molecule comprising: a. providing at least one individual polynucleotide molecule; b. encoding sequence information in the at least one individual

polynucleotide molecule to produce a signal; c. passing at least part of the signal through a channel to produce a received signal comprising nucleotide sequence information about the at least one individual polynucleotide molecule, wherein the received signal comprises noise and/or distortion; d. decoding the received signal to produce a message comprising sequence information about the at least one individual polynucleotide molecule, wherein decoding reduces noise and/or distortion in the message; and e. providing the message to a recipient. In one embodiment the noise comprises incorrect nucleotide calls. In another embodiment distortion comprises uneven amplification of the individual polynucleotide molecule compared with other individual polynucleotide molecules. In another embodiment distortion results from amplification or sequencing bias. In another embodiment the at least one individual polynucleotide molecule is a plurality of individual polynucleotide molecules, and decoding produces a message about each molecule in the plurality. In another embodiment encoding comprises amplifying the at least individual polynucleotide molecule which has optionally been tagged, wherein the signal comprises a collection of amplified molecules. In another embodiment the channel comprises a polynucleotide sequencer and the received signal comprises sequence reads of a plurality of polynucleotides amplified from the at least one individual polynucleotide molecule. In another embodiment decoding comprises grouping sequence reads of amplified molecules amplified from each of the at least one individual polynucleotide molecules. In another embodiment the decoding consists of a probabilistic or statistical method of filtering the generated sequence signal. This disclosure also provides a system comprising a computer readable medium for performing the aforesaid methods.

[0071] In another embodiment the polynucleotides are derived from tumor genomic DNA or RNA. In another embodiment the polynucleotides are derived from cell-free polynucleotides, exosomal polynucleotides, bacterial polynucleotides or viral polynucleotides. In another embodiment further comprising the detection and/or association of affected molecular pathways. In another embodiment further comprising serial monitoring of the health or disease state of an individual. In another embodiment whereby the phylogeny of a genome associated with a disease within an individual is inferred. In another embodiment further comprising diagnosis, monitoring or treatment of a disease. In another embodiment the treatment regimen is selected or modified based on detected polymorphic forms or CNVs or associated pathways. In another embodiment the treatment comprises of a combination therapy.

[0072] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: selecting predefined regions

in a genome; accessing sequence reads and enumerating number of sequence reads in the predefined regions; normalizing the number of sequence reads across the predefined regions; and determining percent of copy number variation in the predefined regions.

[0073] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads; b. filtering out reads that fail to meet a set threshold; c. mapping sequence reads derived from the sequencing onto a reference sequence; d. identifying a subset of mapped sequence reads that align with a variant of the reference sequence at each mappable base position; e. for each mappable base position, calculating a ratio of (a) a number of mapped sequence reads that include a variant as compared to the reference sequence, to (b) a number of total sequence reads for each mappable base position; f. normalizing the ratios or frequency of variance for each mappable base position and determining potential rare variant(s) or other genetic alteration(s); and g. comparing the resulting number for each of the regions with potential rare variant(s) or mutation(s) to similarly derived numbers from a reference sample.

[0074] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; b. collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides.

[0075] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; b. collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides; c. filtering out from among the consensus sequences those that fail to meet a quality threshold.

[0076] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; and i. collapsing the sequence reads by: 1. grouping sequences reads sequenced from amplified progeny polynucleotides

into families, each family amplified from the same tagged parent polynucleotide and, optionally, 2. determining a quantitative measure of sequence reads in each family. In certain embodiments, the executable code further performs the steps of: b. determining a quantitative measure of unique families; c. based on (1) the quantitative measure of unique families and (2) the quantitative measure of sequence reads in each group, inferring a measure of unique tagged parent polynucleotides in the set. In certain embodiments, the executable code further performs the steps of: d. determining a quantitative measure of polymorphic forms among the families; and e. based on the determined quantitative measure of polymorphic forms, inferring a quantitative measure of polymorphic forms in the number of inferred unique tagged parent polynucleotides.

[0077] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides grouping sequences reads sequenced from amplified polynucleotides into families, each family amplified from the same first polynucleotide in the set; b. inferring a quantitative measure of families in the set; c. determining copy number variation by comparing the quantitative measure of families in each set.

[0078] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides grouping the sequence reads into families, each family comprising sequence reads of amplified polynucleotides amplified from the same first polynucleotide; b. inferring, for each set of first polynucleotides, a call frequency for one or more bases in the set of first polynucleotides, wherein inferring comprises: c. assigning, for each family, confidence score for each of a plurality of calls, the confidence score taking into consideration a frequency of the call among members of the family; and d. estimating a frequency of the one or more calls taking into consideration the confidence scores of the one or more calls assigned to each family.

[0079] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data accessing a data file comprising a received signal that comprises endoded sequence information from at least one individual polynucleotide molecule wherein the received signal comprises noise and/or distortion; b. decoding the received signal to produce a message comprising sequence information

about the at least one individual polynucleotide molecule, wherein decoding reduces noise and/or distortion about each individual polynucleotide in the message; and c. writing the message comprising sequence information about the at least one individual polynucleotide molecule to a computer file.

[0080] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; b. collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides; c. filtering out from among the consensus sequences those that fail to meet a quality threshold.

[0081] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; and b. collapsing the sequence reads by: i. grouping sequences reads sequenced from amplified progeny polynucleotides into families, each family amplified from the same tagged parent polynucleotide; and ii. optionally, determining a quantitative measure of sequence reads in each family. In certain embodiments, the executable code further performs the steps of: c. determining a quantitative measure of unique families; d. based on (1) the quantitative measure of unique families and (2) the quantitative measure of sequence reads in each group, inferring a measure of unique tagged parent polynucleotides in the set. In certain embodiments, the executable code further performs the steps of: e. determining a quantitative measure of polymorphic forms among the families; and f. based on the determined quantitative measure of polymorphic forms, inferring a quantitative measure of polymorphic forms in the number of inferred unique tagged parent polynucleotides. In certain embodiments, the executable code further performs the steps of: e. inferring copy number variation for the plurality of sets based on a comparison of the inferred number of tagged parent polynucleotides in each set mapping to each of a plurality of reference sequences.

[0082] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; b. grouping

sequences reads sequenced from amplified polynucleotides into families, each family amplified from the same first polynucleotide in the set; c. inferring a quantitative measure of families in the set; d. determining copy number variation by comparing the quantitative measure of families in each set.

[0083] This disclosure also provides a computer readable medium in non-transitory, tangible form comprising executable code configured to perform the following steps: a. accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides grouping the sequence reads into families, each family comprising sequence reads of amplified polynucleotides amplified from the same first polynucleotide; and b. inferring, for each set of first polynucleotides, a call frequency for one or more bases in the set of first polynucleotides, wherein inferring comprises: i. assigning, for each family, confidence score for each of a plurality of calls, the confidence score taking into consideration a frequency of the call among members of the family; and ii. estimating a frequency of the one or more calls taking into consideration the confidence scores of the one or more calls assigned to each family.

[0084] This disclosure also provides a method comprising: a. providing a sample comprising between 100 and 100,000 haploid human genome equivalents of cell free DNA (cfDNA) polynucleotides; and b. tagging the polynucleotides with between 2 and 1,000,000 unique identifiers. In certain embodiments, the number of unique identifiers is at least 3, at least 5, at least 10, at least 15 or at least 25 and at most 100, at most 1000 or at most 10,000. In certain embodiments, the number of unique identifiers is at most 100, at most 1000, at most 10,000, at most 100,000.

[0085] This disclosure also provides a method comprising: a. providing a sample comprising a plurality of human haploid genome equivalents of fragmented polynucleotides; b. determining z, wherein z is a measure of central tendency (e.g., mean, median or mode) of expected number of duplicate polynucleotides starting at any position in the genome, wherein duplicate polynucleotides have the same start and stop positions; and c. tagging polynucleotides in sample with n unique identifiers, wherein n is between 2 and 100,000*z, 2 and 10,000*z, 2 and 1,000*z or 2 and 100*z.

[0086] This disclosure also provides a method comprising: a. providing at least one set of tagged parent polynucleotides, and for each set of tagged parent polynucleotides; b. producing a plurality of sequence reads for each tagged parent polynucleotide in the set to produce a set of sequencing reads; and c. collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides.

[0087] The disclosure provides for a method for detecting copy number variation comprising: a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide generate a plurality of sequencing reads; b) filtering out reads that fail to meet a set threshold; c) mapping the sequence reads obtained from step (a), after reads are filtered out, to a reference sequence; d) quantifying or enumerating mapped reads in two or more predefined regions of the reference sequence; and e) determining copy number variation in one or more of the predefined regions by: (ii) normalizing number of reads in the predefined regions to each other and/or the number of unique sequence reads in the predefined regions to one another; (ii) comparing the normalized numbers obtained in step (i) to normalized numbers obtained from a control sample.

[0088] The disclosure also provides for a method for detecting a rare mutation in a cell-free or substantially cell free sample obtained from a subject comprising: a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide generate a plurality of sequencing reads; b) performing multiplex sequencing on regions or whole-genome sequencing if enrichment is not performed; c) filtering out reads that fail to meet a set threshold; d) mapping sequence reads derived from the sequencing onto a reference sequence; e) identifying a subset of mapped sequence reads that align with a variant of the reference sequence at each mappable base position; f) for each mappable base position, calculating a ratio of (a) a number of mapped sequence reads that include a variant as compared to the reference sequence, to (b) a number of total sequence reads for each mappable base position; g) normalizing the ratios or frequency of variance for each mappable base position and determining potential rare variant(s) or mutation(s); and h)and comparing the resulting number for each of the regions with potential rare variant(s) or mutation(s) to similarly derived numbers from a reference sample.

[0089] The disclosure also provides for a method of characterizing the heterogeneity of an abnormal condition in a subject, the method comprising generating a genetic profile of extracellular polynucleotides in the subject, wherein the genetic profile comprises a plurality of data resulting from copy number variation and rare mutation analyses.

[0090] In some embodiments, the prevalence/concentration of each rare variant identified in the subject is reported and quantified simultaneously. In some embodiments, a confidence score, regarding the prevalence/concentrations of rare variants in the subject, is reported.

[0091] In some embodiments, the extracellular polynucleotides comprise DNA. In some embodiments, the extracellular polynucleotides comprise RNA.

[0092] In some embodiments, the methods further comprise isolating extracellular polynucleotides from the bodily sample. In some embodiments, the isolating comprises a method for circulating nucleic acid isolation and extraction. In some embodiments, the methods further comprise fragmenting said isolated extracellular polynucleotides. In some embodiments, the bodily sample is selected from the group consisting of blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool and tears.

[0093] In some embodiments, the methods further comprise the step of determining the percent of sequences having copy number variation or rare mutation or variant in said bodily sample. In some embodiments, the determining comprises calculating the percentage of predefined regions with an amount of polynucleotides above or below a predetermined threshold.

[0094] In some embodiments, the subject is suspected of having an abnormal condition. In some embodiments, the abnormal condition is selected from the group consisting of mutations, rare mutations, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection and cancer.

[0095] In some embodiments, the subject is a pregnant female. In some embodiments, the copy number variation or rare mutation or genetic variant is indicative of a fetal abnormality. In some embodiments, the fetal abnormality is selected from the group consisting of mutations, rare mutations, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection and cancer.

[0096] In some embodiments, the methods further comprise attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to sequencing. In some embodiments, each barcode attached to extracellular polynucleotides or fragments thereof prior to sequencing is unique. In some embodiments, each barcode attached to extracellular polynucleotides or fragments thereof prior to sequencing is not unique.

[0097] In some embodiments, the methods further comprise selectively enriching regions from the subject's genome or transcriptome prior to sequencing. In some embodiments, the methods further comprise non-selectively enriching regions from the subject's genome or transcriptome prior to sequencing.

[0098] In some embodiments, the methods further comprise attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to any amplification or enrichment step. In some embodiments, the barcode is a polynucleotide. In some embodiments, the barcode comprises random sequence. In some embodiments, the barcode comprises a fixed or semi-random set of oligonucleotides that in combination with the diversity of molecules sequenced from a select region enables identification of unique molecules. In some embodiments, the barcodes comprise oligonucleotides is at least a 3, 5, 10, 15, 20 25, 30, 35, 40, 45, or 50mer base pairs in length.

[0099] In some embodiments, the methods further comprise amplifying the extracellular polynucleotides or fragments thereof. In some embodiments, the amplification comprises global amplification or whole genome amplification. In some embodiments, the amplification comprises selective amplification. In some embodiments, the amplification comprises non-selective amplification. In some embodiments, suppression amplification or subtractive enrichment is performed.

[00100] In some embodiments, sequence reads of unique identity are detected based on sequence information at the beginning (start) and end (stop) regions of the sequence read and the length of the sequence read. In some embodiments, sequence molecules of unique identity are detected based on sequence information at the beginning (start) and end (stop) regions of the sequence read, the length of the sequence read and attachment of a barcode.

[00101] In some embodiments, the methods further comprise removing a subset of the reads from further analysis prior to quantifying or enumerating reads. In some embodiments, removing comprises filtering out reads with an accuracy or quality score of less than a threshold, e.g., 90%, 99%, 99.9%, or 99.99% and/or mapping score less than a threshold, e.g., 90%, 99%, 99.9% or 99.99%. In some embodiments, the methods further comprise filtering reads with a quality score lower than a set threshold.

[00102] In some embodiments, the predefined regions are uniform or substantially uniform in size. In some embodiments, the predefined regions are at least about 10kb, 20kb, 30kb 40kb, 50kb, 60kb, 70kb, 80kb, 90kb, or 100kb in size.

[00103] In some embodiments, at least 50, 100, 200, 500, 1000, 2000, 5000, 10,000, 20,000, or 50,000 regions are analyzed.

[00104] In some embodiments, the variant occurs in a region of the genome selected from the group consisting of gene fusions, gene duplications, gene deletions, gene translocations, microsatellite regions, gene fragments or combination thereof. In some embodiments, the variant occurs in a region of the genome selected from the group consisting of genes, oncogenes, tumor suppressor genes, promoters, regulatory sequence elements, or combination thereof. In some embodiments, the variant is a nucleotide variant, single base substitution, small indel, transversion, translocation, inversion, deletion, truncation or gene truncation of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15 or 20 nucleotides in length.

[00105] In some embodiments, the methods further comprise correcting/normalizing/adjusting the quantity of mapped reads using the barcodes or unique properties of individual reads. In some embodiments, enumerating the reads is performed through enumeration of unique barcodes in each of the predefined regions and normalizing those numbers across at least a subset of predefined regions that were sequenced.

[00106] In some embodiments, samples at succeeding time intervals from the same subject are analyzed and compared to previous sample results. In some embodiments, the method further comprises amplifying the barcode-attached extracellular polynucleotides. In some embodiments, the methods further comprise determining partial copy number variation frequency, determining loss of heterozygosity, performing gene expression analysis, performing epigenetic analysis and/or performing hypermethylation analysis.

[00107] The disclosure also provides for a method comprising determining copy number variation or performing rare mutation analysis in a cell-free or substantially cell free sample obtained from a subject using multiplex sequencing.

[00108] In some embodiments, the multiplex sequencing comprises performing over 10,000 sequencing reactions. In some embodiments, the multiplex sequencing comprises simultaneously sequencing at least 10,000 different reads. In some embodiments, the multiplex sequencing comprising performing data analysis on at least 10,000 different reads across the genome. In some embodiments, the normalizing and detection is performed using one or more of hidden markov, dynamic programming, support vector machine, Bayesian or probabilistic modeling, trellis decoding, Viterbi decoding, expectation maximization, Kalman filtering, or neural network methodologies. In some embodiments, the methods further comprise monitoring disease progression, monitoring

residual disease, monitoring therapy, diagnosing a condition, prognosing a condition, or selecting a therapy based on discovered variants for the subject. In some embodiments, a therapy is modified based on the most recent sample analysis. In some embodiments, the genetic profile of a tumor, infection or other tissue abnormality is inferred.

[00109] In some embodiments, the growth, remission or evolution of a tumor, infection or other tissue abnormality is monitored. In some embodiments, sequences related to the subject's immune system are analyzed and monitored at single instances or over time. In some embodiments, identification of a variant is followed up through an imaging test (e.g., CT, PET-CT, MRI, X-ray, ultrasound) for localization of the tissue abnormality suspected of causing the identified variant. In some embodiments, the analysis further comprises use of genetic data obtained from a tissue or tumor biopsy from the same patient. In some embodiments, the phylogenetics of a tumor, infection or other tissue abnormality is inferred. In some embodiments, the method further comprises performing population-based no-calling and identification of low-confidence regions. In some embodiments, obtaining the measurement data for the sequence coverage comprises measuring sequence coverage depth at every position of the genome. In some embodiments, correcting the measurement data for the sequence coverage bias comprises calculating window-averaged coverage. In some embodiments, correcting the measurement data for the sequence coverage bias comprises performing adjustments to account for GC bias in the library construction and sequencing process. In some embodiments, correcting the measurement data for the sequence coverage bias comprises performing adjustments based on additional weighting factor associated with individual mappings to compensate for bias.

[00110] In some embodiments, extracellular polynucleotide is derived from a diseased cell origin. In some embodiments, extracellular polynucleotide is derived from a healthy cell origin.

[00111] The disclosure also provides for a system comprising a computer readable medium for performing the following steps: selecting predefined regions in a genome; enumerating number of sequence reads in the predefined regions; normalizing the number of sequence reads across the predefined regions; and determining percent of copy number variation in the predefined regions.

[00112] In some embodiments, the entirety of the genome or at least 85% of the genome is analyzed. In some embodiments, the computer readable medium provides data on percent cancer DNA or RNA in plasma or serum to the end user. In some embodiments, the copy number variants identified are fractional (i.e., non-integer levels) due to heterogeneity in the sample. In some embodiments, enrichment of selected regions is performed. In some embodiments, copy number

variation information is simultaneously extracted based on the methods described herein. In some embodiments, the methods comprise an initial step of polynucleotide bottlenecking to limit the number of starting initial copies or diversity of polynucleotides in the sample.

[00113] The disclosure also provides for a method for detecting a rare mutation in a cell-free or a substantially cell free sample obtained from a subject comprising: a) sequencing extracellular polynucleotides from a bodily sample of a subject, wherein each of the extracellular polynucleotides generate a plurality of sequencing reads; b) filtering out reads that fail to meet a set quality threshold; c) mapping sequence reads derived from the sequencing onto a reference sequence; d) identifying a subset of mapped sequence reads that align with a variant of the reference sequence at each mappable base position; e) for each mappable base position, calculating a ratio of (a) a number of mapped sequence reads that include a variant as compared to the reference sequence, to (b) a number of total sequence reads for each mappable base position; f) normalizing the ratios or frequency of variance for each mappable base position and determining potential rare variant(s) or other genetic alteration(s); and g) comparing the resulting number for each of the regions with potential rare variant(s) or mutation(s) to similarly derived numbers from a reference sample.

[00114] The disclosure also provides for a method comprising: a) providing at least one set of tagged parent polynucleotides, and for each set of tagged parent polynucleotides; b) amplifying the tagged parent polynucleotides in the set to produce a corresponding set of amplified progeny polynucleotides; c) sequencing a subset (including a proper subset) of the set of amplified progeny polynucleotides, to produce a set of sequencing reads; and d) collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides.

[00115] In some embodiments, each polynucleotide in a set is mappable to a reference sequence. In some embodiments, the methods comprise providing a plurality of sets of tagged parent polynucleotides, wherein each set is mappable to a different mappable position in the reference sequence. In some embodiments, the method further comprises: e) analyzing the set of consensus sequences for each set of tagged parent molecules separately or in combination. In some embodiments, the method further comprises converting initial starting genetic material into the tagged parent polynucleotides. In some embodiments, the initial starting genetic material comprises no more than 100 ng of polynucleotides. In some embodiments, the method comprises bottlenecking the initial starting genetic material prior to converting. In some embodiments, the method comprises converting the initial starting genetic material into tagged parent polynucleotides with a conversion

efficiency of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 80% or at least 90%. In some embodiments, the converting comprises any of blunt-end ligation, sticky end ligation, molecular inversion probes, PCR, ligation-based PCR, single strand ligation and single strand circularization. In some embodiments, the initial starting genetic material is cell-free nucleic acid. In some embodiments, a plurality of the sets map to different mappable positions in a reference sequence from the same genome.

[00116] In some embodiments, each tagged parent polynucleotide in the set is uniquely tagged. In some embodiments, each set of parent polynucleotides is mappable to a position in a reference sequence, and the polynucleotides in each set are not uniquely tagged. In some embodiments, the generation of consensus sequences is based on information from the tag and/or at least one of (i) sequence information at the beginning (start) region of the sequence read, (ii) the end (stop) regions of the sequence read and (iii) the length of the sequence read.

[00117] In some embodiments, the method comprises sequencing a subset of the set of amplified progeny polynucleotides sufficient to produce sequence reads for at least one progeny from of each of at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% at least 95%, at least 98%, at least 99%, at least 99.9% or at least 99.99% of unique polynucleotides in the set of tagged parent polynucleotides. In some embodiments, the at least one progeny is a plurality of progeny, e.g., at least 2, at least 5 or at least 10 progeny. In some embodiments, the number of sequence reads in the set of sequence reads is greater than the number of unique tagged parent polynucleotides in the set of tagged parent polynucleotides. In some embodiments, the subset of the set of amplified progeny polynucleotides sequenced is of sufficient size so that any nucleotide sequence represented in the set of tagged parent polynucleotides at a percentage that is the same as the percentage per-base sequencing error rate of the sequencing platform used, has at least a 50%, at least a 60%, at least a 70%, at least a 80%, at least a 90% at least a 95%, at least a 98%, at least a 99%, at least a 99.9% or at least a 99.99% chance of being represented among the set of consensus sequences.

[00118] In some embodiments, the method comprises enriching the set of amplified progeny polynucleotides for polynucleotides mapping to one or more selected mappable positions in a reference sequence by: (i) selective amplification of sequences from initial starting genetic material converted to tagged parent polynucleotides; (ii) selective amplification of tagged parent polynucleotides; (iii) selective sequence capture of amplified progeny polynucleotides; or (iv) selective sequence capture of initial starting genetic material.

[00119] In some embodiments, analyzing comprises normalizing a measure (e.g., number) taken from a set of consensus sequences against a measure taken from a set of consensus sequences from a control sample. In some embodiments, analyzing comprises detecting mutations, rare mutations, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection or cancer.

[00120] In some embodiments, the polynucleotides comprise DNA, RNA, a combination of the two, or DNA plus RNA-derived cDNA. In some embodiments, a certain subset of polynucleotides is selected for, or is enriched based on, polynucleotide length in base-pairs from the initial set of polynucleotides or from the amplified polynucleotides. In some embodiments, analysis further comprises detection and monitoring of an abnormality or disease within an individual, such as, infection and/or cancer. In some embodiments, the method is performed in combination with immune repertoire profiling. In some embodiments, the polynucleotides are extracted from a sample selected from the group consisting of blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool, and tears. In some embodiments, collapsing comprises detecting and/or correcting errors, nicks or lesions present in the sense or anti-sense strand of the tagged parent polynucleotides or amplified progeny polynucleotides.

[00121] The disclosure also provides for a method comprising detecting genetic variation in non-uniquely tagged initial starting genetic material with a sensitivity of at least 5%, at least 1%, at least 0.5%, at least 0.1% or at least 0.05%.

[00122] In some embodiments, the initial starting genetic material is provided in an amount less than 100 ng of nucleic acid, the genetic variation is copy number/heterozygosity variation and detecting is performed with sub-chromosomal resolution; e.g., at least 100 megabase resolution, at least 10 megabase resolution, at least 1 megabase resolution, at least 100 kilobase resolution, at least 10 kilobase resolution or at least 1 kilobase resolution. In some embodiments, the method comprises providing a plurality of sets of tagged parent polynucleotides, wherein each set is mappable to a different mappable position in a reference sequence. In some embodiments, the mappable position in the reference sequence is the locus of a tumor marker and analyzing comprises detecting the tumor marker in the set of consensus sequences.

[00123] In some embodiments, the tumor marker is present in the set of consensus sequences at a frequency less than the error rate introduced at the amplifying step. In some embodiments, the at least one set is a plurality of sets, and the mappable position of the reference sequence comprise a plurality of mappable positions in the reference sequence, each of which mappable position is the locus of a tumor marker. In some embodiments, analyzing comprises detecting copy number variation of consensus sequences between at least two sets of parent polynucleotides. In some embodiments, analyzing comprises detecting the presence of sequence variations compared with the reference sequences.

[00124] In some embodiments, analyzing comprises detecting the presence of sequence variations compared with the reference sequences and detecting copy number variation of consensus sequences between at least two sets of parent polynucleotides. In some embodiments, collapsing comprises: (i) grouping sequences reads sequenced from amplified progeny polynucleotides into families, each family amplified from the same tagged parent polynucleotide; and (ii) determining a consensus sequence based on sequence reads in a family.

[00125] The disclosure also provides for a system comprising a computer readable medium for performing the following steps: a) accepting at least one set of tagged parent polynucleotides, and for each set of tagged parent polynucleotides; b) amplifying the tagged parent polynucleotides in the set to produce a corresponding set of amplified progeny polynucleotides; c) sequencing a subset (including a proper subset) of the set of amplified progeny polynucleotides, to produce a set of sequencing reads; d) collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides and, optionally, e) analyzing the set of consensus sequences for each set of tagged parent molecules.

[00126] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 10% of the individual's genome is sequenced.

[00127] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 20% of the individual's genome is sequenced.

[00128] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 30% of the individual's genome is sequenced.

[00129] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 40% of the individual's genome is sequenced.

[00130] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 50% of the individual's genome is sequenced.

[00131] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 60% of the individual's genome is sequenced.

[00132] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 70% of the individual's genome is sequenced.

[00133] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 80% of the individual's genome is sequenced.

[00134] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration or amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 90% of the individual's genome is sequenced.

[00135] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 10% of the individual's genome is sequenced.

[00136] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 20% of the individual's genome is sequenced.

[00137] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 30% of the individual's genome is sequenced.

[00138] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 40% of the individual's genome is sequenced.

[00139] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 50% of the individual's genome is sequenced.

[00140] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 60% of the individual's genome is sequenced.

[00141] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 70% of the individual's genome is sequenced.

[00142] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 80% of the individual's genome is sequenced.

[00143] The disclosure also provides for a method comprising detecting the presence or absence of genetic alteration and amount of genetic variation in an individual, wherein the detecting is performed with the aid of sequencing of cell-free nucleic acid, wherein at least 90% of the individual's genome is sequenced.

[00144] In some embodiments, the genetic alteration is copy number variation or one or more rare mutations. In some embodiments, the genetic variation comprises one or more causal variants and one or more polymorphisms. In some embodiments, the genetic alteration and/or amount of genetic variation in the individual may be compared to a genetic alteration and/or amount of genetic variation in one or more individuals with a known disease. In some embodiments, the genetic alteration and/or amount of genetic variation in the individual may be compared to a genetic alteration and/or amount of genetic variation in one or more individuals, without a disease. In some embodiments, the cell-free nucleic acid is DNA. In some embodiments, the cell-free nucleic acid is RNA. In some embodiments, the cell-free nucleic acid is DNA and RNA. In some embodiments, the disease is cancer or pre-cancer. In some embodiments, the method further comprising diagnosis or treatment of a disease.

[00145] The disclosure also provides for a method comprising: a) providing at least one set of tagged parent polynucleotides, and for each set of tagged parent polynucleotides; b) amplifying the tagged parent polynucleotides in the set to produce a corresponding set of amplified progeny polynucleotides; c) sequencing a subset (including a proper subset) of the set of amplified progeny polynucleotides, to produce a set of sequencing reads; d) collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides; and e) filtering out from among the consensus sequences those that fail to meet a quality threshold.

[00146] In some embodiments, the quality threshold considers a number of sequence reads from amplified progeny polynucleotides collapsed into a consensus sequence. In some embodiments, the quality threshold considers a number of sequence reads from amplified progeny polynucleotides collapsed into a consensus sequence.

[00147] The disclosure also provides for a system comprising a computer readable medium for performing the methods described herein.

[00148] The disclosure also provides for a method comprising: a) providing at least one set of tagged parent polynucleotides, wherein each set maps to a different mappable position in a reference sequence in one or more genomes, and, for each set of tagged parent polynucleotides; i) amplifying the first polynucleotides to produce a set of amplified polynucleotides; ii) sequencing a subset of the set of amplified polynucleotides, to produce a set of sequencing reads; and iii) collapsing the sequence reads by: (1)grouping sequences reads sequenced from amplified progeny polynucleotides into families, each family amplified from the same tagged parent polynucleotide.

[00149] In some embodiments, collapsing further comprises determining a quantitative measure of sequence reads in each family. In some embodiments, the method further comprises: a) determining a quantitative measure of unique families; and b) based on (1) the quantitative measure of unique families and (2) the quantitative measure of sequence reads in each group, inferring a measure of unique tagged parent polynucleotides in the set. In some embodiments, inferring is performed using statistical or probabilistic models. In some embodiments, the at least one set is a plurality of sets. In some embodiments, the method further comprises correcting for amplification or representational bias between the two sets. In some embodiments, the method further comprises using a control or set of control samples to correct for amplification or representational biases between the two sets. In some embodiments, the method further comprises determining copy number variation between the sets.

[00150] In some embodiments, the method further comprises: d) determining a quantitative measure of polymorphic forms among the families; and e) based on the determined quantitative measure of polymorphic forms, inferring a quantitative measure of polymorphic forms in the number of inferred unique tagged parent polynucleotides. In some embodiments, polymorphic forms include but are not limited to: substitutions, insertions, deletions, inversions, microsatellite changes, transversions, translocations, fusions, methylation, hypermethylation, hyrdroxymethylation, acetylation, epigenetic variants, regulatory-associated variants or protein binding sites.

[00151] In some embodiments, the sets derive from a common sample, and the method further comprises: d) inferring copy number variation for the plurality of sets based on a comparison of the inferred number of tagged parent polynucleotides in each set mapping to each of a plurality of mappable positions in a reference sequence. In some embodiments, the original number of polynucleotides in each set is further inferred. In some embodiments, at least a subset of the tagged parent polynucleotides in each set are non-uniquely tagged.

[00152] The disclosure also provides for a method of determining copy number variation in a sample that includes polynucleotides, the method comprising: a) providing at least two sets of first polynucleotides, wherein each set maps to a different mappable position in a reference sequence in a genome, and, for each set of first polynucleotides; (i) amplifying the polynucleotides to produce a set of amplified polynucleotides; (ii) sequencing a subset of the set of amplified polynucleotides, to produce a set of sequencing reads; (iii) grouping sequences reads sequenced from amplified polynucleotides into families, each family amplified from the same first polynucleotide in the set; (iv)

inferring a quantitative measure of families in the set; and b) determining copy number variation by comparing the quantitative measure of families in each set.

[00153] The disclosure also provides for a method of inferring frequency of sequence calls in a sample of polynucleotides comprising: a) providing at least one set of first polynucleotides, wherein each set maps to a different mappable position in a reference sequence in one or more genomes, and, for each set of first polynucleotides; (i) amplifying the first polynucleotides to produce a set of amplified polynucleotides; (ii) sequencing a subset of the set of amplified polynucleotides, to produce a set of sequencing reads; (iii) grouping the sequence reads into families, each family comprising sequence reads of amplified polynucleotides amplified from the same first polynucleotide; b) inferring, for each set of first polynucleotides, a call frequency for one or more bases in the set of first polynucleotides, wherein inferring comprises: (i) assigning, for each family, confidence score for each of a plurality of calls, the confidence score taking into consideration a frequency of the call among members of the family; and (ii) estimating a frequency of the one or more calls taking into consideration the confidence scores of the one or more calls assigned to each family.

[00154] The disclosure also provides for a method of communicating sequence information about at least one individual polynucleotide molecule, comprising: a) providing at least one individual polynucleotide molecule; b) encoding sequence information in the at least one individual polynucleotide molecule to produce a signal; c) passing at least part of the signal through a channel to produce a received signal comprising nucleotide sequence information about the at least one individual polynucleotide molecule, wherein the received signal comprises noise and/or distortion; d) decoding the received signal to produce a message comprising sequence information about the at least one individual polynucleotide molecule, wherein decoding reduces noise and/or distortion about each individual polynucleotide in the message; and e) providing the message comprising sequence information about the at least one individual polynucleotide molecule to a recipient.

[00155] In some embodiments, the noise comprises incorrect nucleotide calls. In some embodiments, distortion comprises uneven amplification of the individual polynucleotide molecule compared with other individual polynucleotide molecules. In some embodiments, distortion results from amplification or sequencing bias. In some embodiments, the at least one individual polynucleotide molecule is a plurality of individual polynucleotide molecules, and decoding produces a message about each molecule in the plurality. In some embodiments, encoding comprises amplifying the at least one individual polynucleotide molecule, which has optionally been tagged, wherein the signal comprises a collection of amplified molecules. In some embodiments, the channel

comprises a polynucleotide sequencer and the received signal comprises sequence reads of a plurality of polynucleotides amplified from the at least one individual polynucleotide molecule. In some embodiments, decoding comprises grouping sequence reads of amplified molecules amplified from each of the at least one individual polynucleotide molecules. In some embodiments, the decoding consists of a probabilistic or statistical method of filtering the generated sequence signal.

[00156] In some embodiments, the polynucleotides are derived from tumor genomic DNA or RNA. In some embodiments, the polynucleotides are derived from cell-free polynucleotides, exosomal polynucleotides, bacterial polynucleotides or viral polynucleotides. In some embodiments of any of the methods herein, the method further comprises the detection and/or association of affected molecular pathways. In some embodiments of any of the methods herein, the method further comprises serial monitoring of the health or disease state of an individual. In some embodiments the phylogeny of a genome associated with a disease within an individual is inferred. In some embodiments, any of the methods described herein further comprise diagnosis, monitoring or treatment of a disease. In some embodiments, the treatment regimen is selected or modified based on detected polymorphic forms or CNVs or associated pathways. In some embodiments, the treatment comprises of a combination therapy. In some embodiments, the diagnosis further comprises localizing the disease using a radiographic technique, such as, a CT-Scan, PET-CT, MRI, Ultrasound, Ultraound with microbubbles, etc.

[00157] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: selecting predefined regions in a genome; accessing sequence reads and enumerating number of sequence reads in the predefined regions; normalizing the number of sequence reads across the predefined regions; and determining percent of copy number variation in the predefined regions.

[00158] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: accessing a data file comprising a plurality of sequencing reads; filtering out reads that fail to meet a set threshold; mapping sequence reads derived from the sequencing onto a reference sequence; identifying a subset of mapped sequence reads that align with a variant of the reference sequence at each mappable base position; for each mappable base position, calculating a ratio of (a) a number of mapped sequence reads that include a variant as compared to the reference sequence, to (b) a number of total sequence reads for each mappable base position;

normalizing the ratios or frequency of variance for each mappable base position and determining potential rare variant(s) or other genetic alteration(s); and comparing the resulting number for each of the regions with potential rare variant(s) or mutation(s) to similarly derived numbers from a reference sample.

[00159] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; and b) collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides.

[00160] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; b) collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides; and c) filtering out from among the consensus sequences those that fail to meet a quality threshold.

[00161] A computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; and i) collapsing the sequence reads by: (1) grouping sequences reads sequenced from amplified progeny polynucleotides into families, each family amplified from the same tagged parent polynucleotide and, optionally, (2) determining a quantitative measure of sequence reads in each family.

[00162] In some embodiments, the executable code, upon execution by a computer processor, further performs the steps of: b) determining a quantitative measure of unique families; and c) based on (1) the quantitative measure of unique families and (2) the quantitative measure of sequence reads in each group, inferring a measure of unique tagged parent polynucleotides in the set.

[00163] In some embodiments, the executable code, upon execution by a computer processor, further performs the steps of: d) determining a quantitative measure of polymorphic forms among the families; and e) based on the determined quantitative measure of polymorphic forms, inferring a quantitative measure of polymorphic forms in the number of inferred unique tagged parent polynucleotides.

[00164] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides grouping sequences reads sequenced from amplified polynucleotides into families, each family amplified from the same first polynucleotide in the set; b) inferring a quantitative measure of families in the set; and c) determining copy number variation by comparing the quantitative measure of families in each set.

[00165] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides grouping the sequence reads into families, each family comprising sequence reads of amplified polynucleotides amplified from the same first polynucleotide; b) inferring, for each set of first polynucleotides, a call frequency for one or more bases in the set of first polynucleotides, wherein inferring comprises: c) assigning, for each family, confidence score for each of a plurality of calls, the confidence score taking into consideration a frequency of the call among members of the family; and d) estimating a frequency of the one or more calls taking into consideration the confidence scores of the one or more calls assigned to each family.

[00166] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a received signal that comprises endoded sequence information from at least one individual polynucleotide molecule wherein the received signal comprises noise and/or distortion; b) decoding the received signal to produce a message comprising sequence information about the at least one individual polynucleotide molecule, wherein decoding reduces noise and/or distortion about each individual polynucleotide in the

message; and c) writing the message comprising sequence information about the at least one individual polynucleotide molecule to a computer file.

[00167] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; b) collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides; and c) filtering out from among the consensus sequences those that fail to meet a quality threshold.

[00168] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; and b) collapsing the sequence reads by: (i) grouping sequences reads sequenced from amplified progeny polynucleotides into families, each family amplified from the same tagged parent polynucleotide; and (ii) optionally, determining a quantitative measure of sequence reads in each family.

[00169] In some embodiments, the executable code, upon execution by a computer processor, further performs the steps of: d) determining a quantitative measure of unique families;e) based on (1) the quantitative measure of unique families and (2) the quantitative measure of sequence reads in each group, inferring a measure of unique tagged parent polynucleotides in the set.

[00170] In some embodiments, the executable code, upon execution by a computer processor, further performs the steps of: e) determining a quantitative measure of polymorphic forms among the families; and f) based on the determined quantitative measure of polymorphic forms, inferring a quantitative measure of polymorphic forms in the number of inferred unique tagged parent polynucleotides.

[00171] In some embodiments, the the executable code, upon execution by a computer processor, further performs the steps of: e) inferring copy number variation for the plurality of sets based on a comparison of the inferred number of tagged parent polynucleotides in each set mapping to each of a plurality of reference sequences.

[00172] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: a) accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides; b) grouping sequences reads sequenced from amplified polynucleotides into families, each family amplified from the same first polynucleotide in the set; c) inferring a quantitative measure of families in the set; d) determining copy number variation by comparing the quantitative measure of families in each set.

[00173] The disclosure also provides for a computer readable medium comprising non-transitory machine-executable code that, upon execution by a computer processor, implements a method, the method comprising: accessing a data file comprising a plurality of sequencing reads, wherein the sequence reads derive from a set of progeny polynucleotides amplified from at least one set of tagged parent polynucleotides grouping the sequence reads into families, each family comprising sequence reads of amplified polynucleotides amplified from the same first polynucleotide; and inferring, for each set of first polynucleotides, a call frequency for one or more bases in the set of first polynucleotides, wherein inferring comprises: (i) assigning, for each family, confidence score for each of a plurality of calls, the confidence score taking into consideration a frequency of the call among members of the family; and (ii) estimating a frequency of the one or more calls taking into consideration the confidence scores of the one or more calls assigned to each family.

[00174] The disclosure also provides for a composition comprising between 100 and 100,000 human haploid genome equivalents of cfDNA polynucleotides, wherein the polynucleotides are tagged with between 2 and 1,000,000 unique identifiers.

[00175] In some embodiments, the composition comprises between 1000 and 50,000 haploid human genome equivalents of cfDNA polynucleotides, wherein the polynucleotides are tagged with between 2 and 1,000 unique identifiers. In some embodiments, the unique identifiers comprise nucleotide barcodes. The disclosure also provides for a method comprising: a) providing a sample comprising between 100 and 100,000 haploid human genome equivalents of cfDNA polynucleotides; and b) tagging the polynucleotides with between 2 and 1,000,000 unique identifiers.

[00176] The disclosure also provides for a method comprising: a) providing a sample comprising a plurality of human haploid genome equivalents of fragmented polynucleotides; b) determining z, wherein z is a measure of central tendency (e.g., mean, median or mode) of expected

number of duplicate polynucleotides starting at any position in the genome, wherein duplicate polynucleotides have the same start and stop positions; and c) tagging polynucleotides in sample with n unique identifiers, wherein n is between 2 and 100,000*z, 2 and 10,000*z, 2 and 1,000*z or 2 and 100*z. The disclosure also provides for a method comprising: a) providing at least one set of tagged parent polynucleotides, and for each set of tagged parent polynucleotides; b) producing a plurality of sequence reads for each tagged parent polynucleotide in the set to produce a set of sequencing reads; and c) collapsing the set of sequencing reads to generate a set of consensus sequences, each consensus sequence corresponding to a unique polynucleotide among the set of tagged parent polynucleotides.

[00177] The disclosure also provides for a system comprising a computer readable medium comprising machine-executable code as described herein. The disclosure also provides for a system comprising a computer readable medium comprising machine-executable code that, upon execution by a computer processor, implements a method as described herein.

[00178] Additional aspects and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative embodiments of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different embodiments, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[00179] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[00180] The novel features of a system and methods of this disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of this disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of a systems and methods of this disclosure are utilized, and the accompanying drawings of which:

[00181] **FIG. 1** is a flow chart representation of a method of detection of copy number variation using a single sample.

[00182] **FIG. 2** is a flow chart representation of a method of detection of copy number variation using paired samples.

[00183] **FIG. 3** is a flow chart representation of a method of detection of rare mutations (e.g., single nucleotide variants).

[00184] **FIG. 4A** is graphical copy number variation detection report generated from a normal, non cancerous subject.

[00185] **FIG. 4B** is a graphical copy number variation detection report generated from a subject with prostate cancer.

[00186] **FIG. 4C** is schematic representation of internet enabled access of reports generated from copy number variation analysis of a subject with prostate cancer.

[00187] **FIG. 5A** is a graphical copy number variation detection report generated from a subject with prostate cancer remission.

[00188] **FIG. 5B** is a graphical copy number variation detection report generated from a subject with prostate recurrence cancer.

[00189] **FIG. 6A** is graphical detection report (e.g., for single nucleotide variants) generated from various mixing experiments using DNA samples containing both wildtype and mutant copies of MET and TP53.

[00190] **FIG. 6B** is logarithmic graphical representation of (e.g., single nucleotide variant) detection results. Observed vs. expected percent cancer measurements are shown for various mixing experiments using DNAs samples containing both wildtype and mutant copies of MET, HRAS and TP53.

[00191] **FIG. 7A** is graphical report of percentage of two (e.g., single nucleotide variants) in two genes, PIK3CA and TP53, in a subject with prostate cancer as compared to a reference (control).

[00192] **FIG. 7B** is schematic representation of internet enabled access of reports generated from (e.g., single nucleotide variant) analysis of a subject with prostate cancer.

[00193] **FIG. 8** is a flow chart representation of a method of analyzing genetic material.

[00194] **FIG. 9** is a flow chart representation of a method of decoding information in a set of sequence reads to produce, with reduced noise and/or distortion, a representation of information in a set of tagged parent polynucleotides.

[00195] **FIG. 10** is a flow chart representation of a method of reducing distortion in the determination of CNV from a set of sequence reads.

[00196] **FIG. 11** is a flow chart representation of a method of estimating frequency of a base or sequence of bases at a locus in a tagged parent polynucleotide population from a set of sequence reads.

[00197] **FIG. 12** shows a method of communicating sequence information.

[00198] **FIG. 13A and 13B** show detected minor allele frequencies across an entire 70kb panel in 0.3% LNCaP cfDNA titration using standard sequencing and Digital Sequencing workflows. Standard "analog" sequencing (Fig. 13A) masks all true-positive rare variants in tremendous noise due to PCR and sequencing errors despite Q30 filtering. Digital Sequencing (Fig. 13B) eliminates all PCR and sequencing noise, revealing true mutations with no false positives: green circles are SNP points in normal cfDNA and red circles are detected LNCaP mutations.

[00199] **FIG. 14:** Shows titration of LNCap cfDNA.

[00200] **FIG. 15** shows a computer system that is programmed or otherwise configured to implement various methods of the present disclosure.

DETAILED DESCRIPTION OF THE INVENTION

I. General Overview

[00201] The present disclosure provides a system and method for the detection of rare mutations (e.g., single or multiple nucleotide variations) and copy number variations in cell free polynucleotides. Generally, the systems and methods comprise sample preparation, or the extraction and isolation of cell free polynucleotide sequences from a bodily fluid; subsequent sequencing of cell free polynucleotides by techniques known in the art; and application of bioinformatics tools to detect rare mutations and copy number variations as compared to a reference. The systems and methods also may contain a database or collection of different rare mutations or copy number variation profiles of different diseases, to be used as additional references in aiding detection of rare mutations (e.g., single nucleotide variation profiling), copy number variation profiling or general genetic profiling of a disease.

[00202] The systems and methods may be particularly useful in the analysis of cell free DNAs. In some cases, cell free DNA are extracted and isolated from a readily accessible bodily fluid such as blood. For example, cell free DNA can be extracted using a variety of methods known in the art, including but not limited to isopropanol precipitation and/or silica based purification. Cell free DNA

may be extracted from any number of subjects, such as subjects without cancer, subjects at risk for cancer, or subjects known to have cancer (e.g. through other means).

[00203] Following the isolation/extraction step, any of a number of different sequencing operations may be performed on the cell free polynucleotide sample. Samples may be processed before sequencing with one or more reagents (e.g., enzymes, unique identifiers (e.g., barcodes), probes, etc.). In some cases if the sample is processed with a unique identifier such as a barcode, the samples or fragments of samples may be tagged individually or in subgroups with the unique identifier. The tagged sample may then be used in a downstream application such as a sequencing reaction by which individual molecules may be tracked to parent molecules.

[00204] After sequencing data of cell free polynucleotide sequences is collected, one or more bioinformatics processes may be applied to the sequence data to detect genetic features or aberrations such as copy number variation, rare mutations (e.g., single or multiple nucleotide variations) or changes in epigenetic markers, including but not limited to methylation profiles. In some cases, in which copy number variation analysis is desired, sequence data may be: 1) aligned with a reference genome; 2) filtered and mapped; 3) partitioned into windows or bins of sequence; 4) coverage reads counted for each window; 5) coverage reads can then be normalized using a stochastic or statistical modeling algorithm; 6) and an output file can be generated reflecting discrete copy number states at various positions in the genome. In other cases, in which rare mutation analysis is desired, sequence data may be 1) aligned with a reference genome; 2) filtered and mapped; 3) frequency of variant bases calculated based on coverage reads for that specific base; 4) variant base frequency normalized using a stochastic, statistical or probabilistic modeling algorithm; 5) and an output file can be generated reflecting mutation states at various positions in the genome.

[00205] A variety of different reactions and/operations may occur within the systems and methods disclosed herein, including but not limited to: nucleic acid sequencing, nucleic acid quantification, sequencing optimization, detecting gene expression, quantifying gene expression, genomic profiling, cancer profiling, or analysis of expressed markers. Moreover, the systems and methods have numerous medical applications. For example, it may be used for the identification, detection, diagnosis, treatment, staging of, or risk prediction of various genetic and non-genetic diseases and disorders including cancer. It may be used to assess subject response to different treatments of said genetic and non-genetic diseases, or provide information regarding disease progression and prognosis.

[00206] Polynucleotide sequencing can be compared with a problem in communication theory. An initial individual polynucleotide or ensemble of polynucleotides is thought of as an original message. Tagging and/or amplifying can be thought of as encoding the original message into a signal. Sequencing can be thought of as communication channel. The output of a sequencer, e.g., sequence reads, can be thought of as a received signal. Bioinformatic processing can be thought of as a receiver that decodes the received signal to produce a transmitted message, e.g., a nucleotide sequence or sequences. The received signal can include artifacts, such as noise and distortion. Noise can be thought of as an unwanted random addition to a signal. Distortion can be thought of as an alteration in the amplitude of a signal or portion of a signal.

[00207] Noise can be introduced through errors in copying and/or reading a polynucleotide. For example, in a sequencing process a single polynucleotide can first be subject to amplification. Amplification can introduce errors, so that a subset of the amplified polynucleotides may contain, at a particular locus, a base that is not the same as the original base at that locus. Furthermore, in the reading process a base at any particular locus may be read incorrectly. As a consequence, the collection of sequence reads can include a certain percentage of base calls at a locus that are not the same as the original base. In typical sequencing technologies this error rate can be in the single digits, e.g., 2%-3%. When a collection of molecules that are all presumed to have the same sequence are sequenced, this noise is sufficiently small that one can identify the original base with high reliability.

[00208] However, if a collection of parent polynucleotides includes a subset of polynucleotides having sequence variants at a particular locus, noise can be a significant problem. This can be the case, for example, when cell free DNA includes not only germline DNA, but DNA from another source, such as fetal DNA or DNA from a cancer cell. In this case, if the frequency of molecules with sequence variants is in the same range as the frequency of errors introduced by the sequencing process, then true sequence variants may not be distinguishable from noise. This could interfere, for example, with detecting sequence variants in a sample.

[00209] Distortion can be manifested in the sequencing process as a difference in signal strength, e.g., total number of sequence reads, produced by molecules in a parent population at the same frequency. Distortion can be introduced, for example, through amplification bias, GC bias, or sequencing bias. This could interfere with detecting copy number variation in a sample. GC bias results in the uneven representation of areas rich or poor in GC content in the sequence reading.

[00210] This invention provides methods of reducing sequencing artifacts, such as noise and/or distortion, in a polynucleotide sequencing process. Grouping sequence reads into families derived

from original individual molecules can reduce noise and/or distortion from a single individual molecule or from an ensemble of molecules. With respect to a single molecule, grouping reads into a family reduces distortion by, for example, indicating that many sequence reads actually represent a single molecule rather than many different molecules. Collapsing sequence reads into a consensus sequence is one way to reduce noise in the received message from one molecule. Using probabilistic functions that convert received frequencies is another way. With respect to an ensemble of molecules, grouping reads into families and determining a quantitative measure of the families reduces distortion, for example, in the quantity of molecules at each of a plurality of different loci. Again, collapsing sequence reads of different families into consensus sequences eliminate errors introduced by amplification and/or sequencing error. Furthermore, determining frequencies of base calls based on probabilities derived from family information also reduces noise in the received message from an ensemble of molecules.

[00211] Methods of reducing noise and/or distortion from a sequencing process are known. These include, for example, filtering sequences, e.g., requiring them to meet a quality threshold, or reducing GC bias. Such methods typically are performed on the collection of sequence reads that are the output of a sequencer, and can be performed sequence read-by-sequence read, without regard for family structure (sub-collections of sequences derived from a single original parent molecule). Certain methods of this invention reduce noise and distortion by reducing noise and/or distortion within families of sequence reads, that is, operating on sequence reads grouped into families derived from a single parent polynucleotide molecule. Signal artifact reduction at the family level can produce significantly less noise and distortion in the ultimate message that is provided than artifact reduction performed at a sequence read-by-sequence read level or on sequencer output as a whole.

[00212] The present disclosure further provides methods and systems for detecting with high sensitivity genetic variation in a sample of initial genetic material. The methods involve using one or both of the following tools: First, the efficient conversion of individual polynucleotides in a sample of initial genetic material into sequence-ready tagged parent polynucleotides, so as to increase the probability that individual polynucleotides in a sample of initial genetic material will be represented in a sequence-ready sample. This can produce sequence information about more polynucleotides in the initial sample. Second, high yield generation of consensus sequences for tagged parent polynucleotides by high rate sampling of progeny polynucleotides amplified from the tagged parent polynucleotides, and collapsing of generated sequence reads into consensus sequences representing sequences of parent tagged polynucleotides. This can reduce noise introduced by amplification bias

and/or sequencing errors, and can increase sensitivity of detection. Collapsing is performed on a plurality of sequence reads, generated either from reads of amplified molecules, or multiple reads of a single molecule.

[00213] Sequencing methods typically involve sample preparation, sequencing of polynucleotides in the prepared sample to produce sequence reads and bioinformatic manipulation of the sequence reads to produce quantitative and/or qualitative genetic information about the sample. Sample preparation typically involves converting polynucleotides in a sample into a form compatible with the sequencing platform used. This conversion can involve tagging polynucleotides. In certain embodiments of this invention the tags comprise polynucleotide sequence tags. Conversion methodologies used in sequencing may not be 100% efficient. For example, it is not uncommon to convert polynucleotides in a sample with a conversion efficiency of about 1-5%, that is, about 1-5% of the polynucleotides in a sample are converted into tagged polynucleotides. Polynucleotides that are not converted into tagged molecules are not represented in a tagged library for sequencing. Accordingly, polynucleotides having genetic variants represented at low frequency in the initial genetic material may not be represented in the tagged library and, therefore may not be sequenced or detected. By increasing conversion efficiency, the probability that a rare polynucleotide in the initial genetic material will be represented in the tagged library and, consequently, detected by sequencing is increased. Furthermore, rather than directly address the low conversion efficiency issue of library preparation, most protocols to date call for greater than 1 microgram of DNA as input material. However, when input sample material is limited or detection of polynucleotides with low representation is desired, high conversion efficiency can efficiently sequence the sample and/or to adequately detect such polynucleotides.

[00214] This disclosure provides methods of converting initial polynucleotides into tagged polynucleotides with a conversion efficiency of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 80% or at least 90%. The methods involve, for example, using any of blunt-end ligation, sticky end ligation, molecular inversion probes, PCR, ligation-based PCR, multiplex PCR, single strand ligation and single strand circularization. The methods can also involve limiting the amount of initial genetic material. For example, the amount of initial genetic material can be less than 1 ug, less than 100 ng or less than 10 ng. These methods are described in more detail herein.

[00215] Obtaining accurate quantitative and qualitative information about polynucleotides in a tagged library can result in a more sensitive characterization of the initial genetic material. Typically,

polynucleotides in a tagged library are amplified and the resulting amplified molecules are sequenced. Depending on the throughput of the sequencing platform used, only a subset of the molecules in the amplified library produce sequence reads. So, for example, the number of amplified molecules sampled for sequencing may be about only 50% of the unique polynucleotides in the tagged library. Furthermore, amplification may be biased in favor of or against certain sequences or certain members of the tagged library. This may distort quantitative measurement of sequences in the tagged library. Also, sequencing platforms can introduce errors in sequencing. For example, sequences can have a per-base error rate of 0.5-1%. Amplification bias and sequencing errors introduce noise into the final sequencing product. This noise can diminish sensitivity of detection. For example, sequence variants whose frequency in the tagged population is less than the sequencing error rate can be mistaken for noise. Also, by providing reads of sequences in greater or less amounts than their actual number in a population, amplification bias can distort measurements of copy number variation. Alternatively, a plurality of sequence reads from a single polynucleotide can be produced without amplification. This can be done, for example, with nanopore methods.

[00216] This disclosure provides methods of accurately detecting and reading unique polynucleotides in a tagged pool. In certain embodiments this disclosure provides sequence-tagged polynucleotides that, when amplified and sequenced, or when sequenced a plurality of times to produce a plurality of sequence reads, provide information that allowed the tracing back, or collapsing, of progeny polynucleotides to the unique tag parent polynucleotide molecule. Collapsing families of amplified progeny polynucleotides reduces amplification bias by providing information about original unique parent molecules. Collapsing also reduces sequencing errors by eliminating from sequencing data mutant sequences of progeny molecules.

[00217] Detecting and reading unique polynucleotides in the tagged library can involve two strategies. In one strategy a sufficiently large subset of the amplified progeny polynucleotide pool is a sequenced such that, for a large percentage of unique tagged parent polynucleotides in the set of tagged parent polynucleotides, there is a sequence read that is produced for at least one amplified progeny polynucleotide in a family produced from a unique tagged parent polynucleotide. In a second strategy, the amplified progeny polynucleotide set is sampled for sequencing at a level to produce sequence reads from multiple progeny members of a family derived from a unique parent polynucleotide. Generation of sequence reads from multiple progeny members of a family allows collapsing of sequences into consensus parent sequences.

[00218] So, for example, sampling a number of amplified progeny polynucleotides from the set of amplified progeny polynucleotides that is equal to the number of unique tagged parent polynucleotides in the set of tagged parent polynucleotides (particularly when the number is at least 10,000) will produce, statistically, a sequence read for at least one of progeny of about 68% of the tagged parent polynucleotides in the set, and about 40% of the unique tagged parent polynucleotides in the original set will be represented by at least two progeny sequence reads. In certain embodiments the amplified progeny polynucleotide set is sampled sufficiently so as to produce an average of five to ten sequence reads for each family. Sampling from the amplified progeny set of 10-times as many molecules as the number of unique tagged parent polynucleotides will produce, statistically, sequence information about 99.995% of the families, of which 99.95% of the total families will be covered by a plurality of sequence reads. A consensus sequence can be built from the progeny polynucleotides in each family so as to dramatically reduce the error rate from the nominal per-base sequencing error rate to a rate possibly many orders of magnitude lower. For example, if the sequencer has a random per-base error rate of 1% and the chosen family has 10 reads, a consensus sequence built from these 10 reads would possess an error rate of below 0.0001%. Accordingly, the sampling size of the amplified progeny to be sequenced can be chosen so as to ensure a sequence having a frequency in the sample that is no greater than the nominal per-base sequencing error rate to a rate of the sequencing platform used, has at least 99% chance being represented by at least one read.

[00219] In another embodiment the set of amplified progeny polynucleotides is sampled to a level to produce a high probability e.g., at least 90%, that a sequence represented in the set of tagged parent polynucleotides at a frequency that is about the same as the per base sequencing error rate of the sequencing platform used is covered by at least one sequence read and preferably a plurality of sequence reads. So, for example, if the sequencing platform has a per base error rate of 0.2% in a sequence or set of sequences is represented in the set of tagged parent polynucleotides at a frequency of about 0.2%, then the number of polynucleotides in the amplified progeny pool that are sequenced can be about X times the number of unique molecules in the set of tagged parent polynucleotides.

[00220] These methods can be combined with any of the noise reduction methods described. Including, for example, qualifying sequence reads for inclusion in the pool of sequences used to generate consensus sequences.

[00221] This information can now be used for both qualitative and quantitative analysis. For example, for quantitative analysis, a measure, e.g., a count, of the amount of tagged parent molecules mapping to a reference sequence is determined. This measure can be compared with a measure of

tagged parent molecules mapping to a different genomic region. That is, the amount of tagged parent molecules mapping to a first location or mappable position in a reference sequence, such as the human genome, can be compared with a measure of tagged parent molecules mapping to a second location or mappable position in a reference sequence. This comparison can reveal, for example, the relative amounts of parent molecules mapping to each region. This, in turn, provides an indication of copy number variation for molecules mapping to a particular region. For example, if the measure of polynucleotides mapping to a first reference sequence is greater than the measure of polynucleotides mapping to a second reference sequence, this may indicate that the parent population, and by extension the original sample, included polynucleotides from cells exhibiting aneuploidy. The measures can be normalized against a control sample to eliminate various biases. Quantitative measures can include, for example, number, count, frequency (whether relative, inferred or absolute).

[00222] A reference genome can include the genome of any species of interest. Human genome sequences useful as references can include the hg19 assembly or any previous or available hg assembly. Such sequences can be interrogated using the genome brower available at genome.ucsc.edu/index.html. Other species genomes include, for example PanTro2 (chimp) and mm9 (mouse).

[00223] For qualitative analysis, sequences from a set of tagged polynucleotides mapping to a reference sequence can be analyzed for variant sequences and their frequency in the population of tagged parent polynucleotides can be measured.

II. Sample Preparation

A. Polynucleotide Isolation and Extraction

[00224] The systems and methods of this disclosure may have a wide variety of uses in the manipulation, preparation, identification and/or quantification of cell free polynucleotides. Examples of polynucleotides include but are not limited to: DNA, RNA, amplicons, cDNA, dsDNA, ssDNA, plasmid DNA, cosmid DNA, high Molecular Weight (MW) DNA, chromosomal DNA, genomic DNA, viral DNA, bacterial DNA, mtDNA (mitochondrial DNA), mRNA, rRNA, tRNA, nRNA, siRNA, snRNA, snoRNA, scaRNA, microRNA, dsRNA, ribozyme, riboswitch and viral RNA (e.g., retroviral RNA).

[00225] Cell free polynucleotides may be derived from a variety of sources including human, mammal, non-human mammal, ape, monkey, chimpanzee, reptilian, amphibian, or avian, sources. Further, samples may be extracted from variety of animal fluids containing cell free sequences,

including but not limited to blood, serum, plasma, vitreous, sputum, urine, tears, perspiration, saliva, semen, mucosal excretions, mucus, spinal fluid, amniotic fluid, lymph fluid and the like. Cell free polynucleotides may be fetal in origin (via fluid taken from a pregnant subject), or may be derived from tissue of the subject itself.

[00226] Isolation and extraction of cell free polynucleotides may be performed through collection of bodily fluids using a variety of techniques. In some cases, collection may comprise aspiration of a bodily fluid from a subject using a syringe. In other cases collection may comprise pipetting or direct collection of fluid into a collecting vessel.

[00227] After collection of bodily fluid, cell free polynucleotides may be isolated and extracted using a variety of techniques known in the art. In some cases, cell free DNA may be isolated, extracted and prepared using commercially available kits such as the Qiagen Qiamp® Circulating Nucleic Acid Kit protocol. In other examples, Qiagen Qubit ™ dsDNA HS Assay kit protocol, Agilent™ DNA 1000 kit, or TruSeq™ Sequencing Library Preparation; Low-Throughput (LT) protocol may be used.

[00228] Generally, cell free polynucleotides are extracted and isolated by from bodily fluids through a partitioning step in which cell free DNAs, as found in solution, are separated from cells and other non soluble components of the bodily fluid. Partitioning may include, but is not limited to, techniques such as centrifugation or filtration. In other cases, cells are not partitioned from cell free DNA first, but rather lysed. In this example, the genomic DNA of intact cells is partitioned through selective precipitation. Cell free polynucleotides, including DNA, may remain soluble and may be separated from insoluble genomic DNA and extracted. Generally, after addition of buffers and other wash steps specific to different kits, DNA may be precipitated using isopropanol precipitation. Further clean up steps may be used such as silica based columns to remove contaminants or salts. General steps may be optimized for specific applications. Non specific bulk carrier polynucleotides, for example, may be added throughout the reaction to optimize certain aspects of the procedure such as yield.

[00229] Isolation and purification of cell free DNA may be accomplished using any means, including, but not limited to, the use of commercial kits and protocols provided by companies such as Sigma Aldrich, Life Technologies, Promega, Affymetrix, IBI or the like. Kits and protocols may also be non-commercially available.

[00230] After isolation, in some cases, the cell free polynucleotides are pre-mixed with one or more additional materials, such as one or more reagents (e.g., ligase, protease, polymerase) prior to sequencing.

[00231] One method of increasing conversion efficiency involves using a ligase engineered for optimal reactivity on single-stranded DNA, such as a ThermoPhage ssDNA ligase derivative. Such ligases bypass traditional steps in library preparation of end-repair and A-tailing that can have poor efficiencies and/or accumulated losses due to intermediate cleanup steps, and allows for twice the probability that either the sense or anti-sense starting polynucleotide will be converted into an appropriately tagged polynucleotide. It also converts double-stranded polynucleotides that may possess overhangs that may not be sufficiently blunt-ended by the typical end-repair reaction. Optimal reactions conditions for this ssDNA reaction are: 1 x reaction buffer (50 mM MOPS (pH 7.5), 1 mM DTT, 5 mM MgCl2, 10 mM KCl). With 50 mM ATP, 25 mg/ml BSA, 2.5 mM MnCl2 , 200 pmol 85 nt ssDNA oligomer and 5 U ssDNA ligase incubated at 65°C for 1 hour. Subsequent amplification using PCR can further convert the tagged single-stranded library to a double-stranded library and yield an overall conversion efficiency of well above 20%. Other methods of increasing conversion rate, e.g., to above 10%, include, for example, any of the following, alone or in combination: Annealing-optimized molecular-inversion probes, blunt-end ligation with a well-controlled polynucleotide size range, sticky-end ligation or an upfront multiplex amplification step with or without the use of fusion primers.

B. Molecular Bar Coding of Cell Free Polynucleotides

[00232] The systems and methods of this disclosure may also enable the cell free polynucleotides to be tagged or tracked in order to permit subsequent identification and origin of the particular polynucleotide. This feature is in contrast with other methods that use pooled or multiplex reactions and that only provide measurements or analyses as an average of multiple samples. Here, the assignment of an identifier to individual or subgroups of polynucleotides may allow for a unique identity to be assigned to individual sequences or fragments of sequences. This may allow acquisition of data from individual samples and is not limited to averages of samples.

[00233] In some examples, nucleic acids or other molecules derived from a single strand may share a common tag or identifier and therefore may be later identified as being derived from that strand. Similarly, all of the fragments from a single strand of nucleic acid may be tagged with the same identifier or tag, thereby permitting subsequent identification of fragments from the parent strand. In other cases, gene expression products (e.g., mRNA) may be tagged in order to quantify

expression, by which the barcode, or the barcode in combination with sequence to which it is attached can be counted. In still other cases, the systems and methods can be used as a PCR amplification control. In such cases, multiple amplification products from a PCR reaction can be tagged with the same tag or identifier. If the products are later sequenced and demonstrate sequence differences, differences among products with the same identifier can then be attributed to PCR error.

[00234] Additionally, individual sequences may be identified based upon characteristics of sequence data for the read themselves. For example, the detection of unique sequence data at the beginning (start) and end (stop) portions of individual sequencing reads may be used, alone or in combination, with the length, or number of base pairs of each sequence read unique sequence to assign unique identities to individual molecules. Fragments from a single strand of nucleic acid, having been assigned a unique identity, may thereby permit subsequent identification of fragments from the parent strand. This can be used in conjunction with bottlenecking the initial starting genetic material to limit diversity.

[00235] Further, using unique sequence data at the beginning (start) and end (stop) portions of individual sequencing reads and sequencing read length may be used, alone or combination, with the use of barcodes. In some cases, the barcodes may be unique as described herein. In other cases, the barcodes themselves may not be unique. In this case, the use of non unique barcodes, in combination with sequence data at the beginning (start) and end (stop) portions of individual sequencing reads and sequencing read length may allow for the assignment of a unique identity to individual sequences. Similarly, fragments from a single strand of nucleic acid having been assigned a unique identity, may thereby permit subsequent identification of fragments from the parent strand.

[00236] Generally, the methods and systems provided herein are useful for preparation of cell free polynucleotide sequences to a down-stream application sequencing reaction. Often, a sequencing method is classic Sanger sequencing. Sequencing methods may include, but are not limited to: high-throughput sequencing, pyrosequencing, sequencing-by-synthesis, single-molecule sequencing, nanopore sequencing, semiconductor sequencing, sequencing-by-ligation, sequencing-by-hybridization, RNA-Seq (Illumina), Digital Gene Expression (Helicos), Next generation sequencing, Single Molecule Sequencing by Synthesis (SMSS)(Helicos), massively-parallel sequencing, Clonal Single Molecule Array (Solexa), shotgun sequencing, Maxim-Gilbert sequencing, primer walking, and any other sequencing methods known in the art.

C. Assignment of Barcodes to Cell Free Polynucleotide Sequences

[00237] The systems and methods disclosed herein may be used in applications that involve the assignment of unique or non-unique identifiers, or molecular barcodes, to cell free polynucleotides. Often, the identifier is a bar-code oligonucleotide that is used to tag the polynucleotide; but, in some cases, different unique identifiers are used. For example, in some cases, the unique identifier is a hybridization probe. In other cases, the unique identifier is a dye, in which case the attachment may comprise intercalation of the dye into the analyte molecule (such as intercalation into DNA or RNA) or binding to a probe labeled with the dye. In still other cases, the unique identifier may be a nucleic acid oligonucleotide, in which case the attachment to the polynucleotide sequences may comprise a ligation reaction between the oligonucleotide and the sequences or incorporation through PCR. In other cases, the reaction may comprise addition of a metal isotope, either directly to the analyte or by a probe labeled with the isotope. Generally, assignment of unique or non-unique identifiers, or molecular barcodes in reactions of this disclosure may follow methods and systems described by, for example, US patent applications 20010053519, 20030152490, 20110160078 and US patent US 6,582,908.

[00238] Often, the method comprises attaching oligonucleotide barcodes to nucleic acid analytes through an enzymatic reaction including but not limited to a ligation reaction. For example, the ligase enzyme may covalently attach a DNA barcode to fragmented DNA (e.g., high molecular-weight DNA). Following the attachment of the barcodes, the molecules may be subjected to a sequencing reaction.

[00239] However, other reactions may be used as well. For example, oligonucleotide primers containing barcode sequences may be used in amplification reactions (e.g., PCR, qPCR, reverse-transcriptase PCR, digital PCR, etc.) of the DNA template analytes, thereby producing tagged analytes. After assignment of barcodes to individual cell free polynucleotide sequences, the pool of molecules may be sequenced.

[00240] In some cases, PCR may be used for global amplification of cell free polynucleotide sequences. This may comprise using adapter sequences that may be first ligated to different molecules followed by PCR amplification using universal primers. PCR for sequencing may be performed using any means, including but not limited to use of commercial kits provided by Nugen (WGA kit), Life Technologies, Affymetrix, Promega, Qiagen and the like. In other cases, only certain target molecules within a population of cell free polynucleotide molecules may be amplified.

Specific primers, may in conjunction with adapter ligation, may be used to selectively amplify certain targets for downstream sequencing.

[00241] The unique identifiers (e.g., oligonucleotide bar-codes, antibodies, probes, etc.) may be introduced to cell free polynucleotide sequences randomly or non-randomly. In some cases, they are introduced at an expected ratio of unique identifiers to microwells. For example, the unique identifiers may be loaded so that more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 500, 1000, 5000, 10000, 50,000, 100,000, 500,000, 1,000,000, 10,000,000, 50,000,000 or 1,000,000,000 unique identifiers are loaded per genome sample. In some cases, the unique identifiers may be loaded so that less than about 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 500, 1000, 5000, 10000, 50,000, 100,000, 500,000, 1,000,000, 10,000,000, 50,000,000 or 1,000,000,000 unique identifiers are loaded per genome sample. In some cases, the average number of unique identifiers loaded per sample genome is less than, or greater than, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 500, 1000, 5000, 10000, 50,000, 100,000, 500,000, 1,000,000, 10,000,000, 50,000,000 or 1,000,000,000 unique identifiers per genome sample.

[00242] In some cases, the unique identifiers may be a variety of lengths such that each barcode is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 500, 1000 base pairs. In other cases, the barcodes may comprise less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 50, 100, 500, 1000 base pairs.

[00243] In some cases, unique identifiers may be predetermined or random or semi-random sequence oligonucleotides. In other cases, a plurality of barcodes may be used such that barcodes are not necessarily unique to one another in the plurality. In this example, barcodes may be ligated to individual molecules such that the combination of the bar code and the sequence it may be ligated to creates a unique sequence that may be individually tracked. As described herein, detection of non unique barcodes in combination with sequence data of beginning (start) and end (stop) portions of sequence reads may allow assignment of a unique identity to a particular molecule. The length, or number of base pairs, of an individual sequence read may also be used to assign a unique identity to such a molecule. As described herein, fragments from a single strand of nucleic acid having been assigned a unique identity, may thereby permit subsequent identification of fragments from the parent strand. In this way the polynucleotides in the sample can be uniquely or substantially uniquely tagged.

[00244] The unique identifiers may be used to tag a wide range of analytes, including but not limited to RNA or DNA molecules. For example, unique identifiers (e.g., barcode oligonucleotides) may be attached to whole strands of nucleic acids or to fragments of nucleic acids (e.g., fragmented

genomic DNA, fragmented RNA). The unique identifiers (e.g., oligonucleotides) may also bind to gene expression products, genomic DNA, mitochondrial DNA, RNA, mRNA, and the like.

[00245] In many applications, it may be important to determine whether individual cell free polynucleotide sequences each receive a different unique identifier (e.g., oligonucleotide barcode). If the population of unique identifiers introduced into the systems and methods is not significantly diverse, different analytes may possibly be tagged with identical identifiers. The systems and methods disclosed herein may enable detection of cell free polynucleotide sequences tagged with the same identifier. In some cases, a reference sequences may be included with the population of cell free polynucleotide sequences to be analyzed. The reference sequence may be, for example, a nucleic acid with a known sequence and a known quantity. If the unique identifiers are oligonucleotide barcodes and the analytes are nucleic acids, the tagged analytes may subsequently be sequenced and quantified. These methods may indicate if one or more fragments and/or analytes may have been assigned an identical barcode.

[00246] A method disclosed herein may comprise utilizing reagents necessary for the assignment of barcodes to the analytes. In the case of ligation reactions, reagents including, but not limited to, ligase enzyme, buffer, adapter oligonucleotides, a plurality of unique identifier DNA barcodes and the like may be loaded into the systems and methods. In the case of enrichment, reagents including but not limited to a plurality of PCR primers, oligonucleotides containing unique identifying sequence, or barcode sequence, DNA polymerase, DNTPs, and buffer and the like may be used in preparation for sequencing.

[00247] Generally, the method and system of this disclosure may utilize the methods of US patent US 7,537,897 in using molecular barcodes to count molecules or analytes.

[00248] In a sample comprising fragmented genomic DNA, e.g., cell-free DNA (cfDNA), from a plurality of genomes, there is some likelihood that more than one polynucleotide from different genomes will have the same start and stop positions ("duplicates" or "cognates"). The probable number of duplicates beginning at any position is a function of the number of haploid genome equivalents in a sample and the distribution of fragment sizes. For example, cfDNA has a peak of fragments at about 160 nucleotides, and most of the fragments in this peak range from about 140 nucleotides to 180 nucleotides. Accordingly, cfDNA from a genome of about 3 billion bases (e.g., the human genome) may be comprised of almost 20 million ($2x10^7$) polynucleotide fragments. A sample of about 30 ng DNA can contain about 10,000 haploid human genome equivalents. (Similarly, a sample of about 100 ng of DNA can contain about 30,000 haploid human genome

equivalents.) A sample containing about 10,000 (10^4) haploid genome equivalents of such DNA can have about 200 billion ($2x10^{11}$) individual polynucleotide molecules. It has been empirically determined that in a sample of about 10,000 haploid genome equivalents of human DNA, there are about 3 duplicate polynucleotides beginning at any given position. Thus, such a collection can contain a diversity of about $6x10^{10}$-$8x10^{10}$ (about 60 billion-80 billion e.g., about 70 billion ($7x10^{10}$)) differently sequenced polynucleotide molecules.

[00249] The probability of correctly identifying molecules is dependent on initial number of genome equivalents, the length distribution of sequenced molecules, sequence uniformity and number of tags. When the tag count is equal to one, that is, equivalent to having no unique tags or not tagging. The table below lists the probability of correctly identifying a molecule as unique assuming a typical cell-free size distribution as above.

Tag Count	Tag %Correctly uniquely identified
1000 human haploid genome equivalents	
1	96.9643
4	99.2290
9	99.6539
16	99.8064
25	99.8741
100	99.9685
3000 human haploid genome equivalents	
1	91.7233
4	97.8178
9	99.0198
16	99.4424
25	99.6412
100	99.9107

[00250] In this case, upon sequencing the genomic DNA, it may not be possible to determine which sequence reads are derived from which parent molecules. This problem can be diminished by tagging parent molecules with a sufficient number of unique identifiers (e.g., the tag count) such that there is a likelihood that two duplicate molecules, i.e., molecules having the same start and stop positions, bear different unique identifiers so that sequence reads are traceable back to particular parent molecules. One approach to this problem is to uniquely tag every, or nearly every, different parent molecule in the sample. However, depending on the number of haploid gene equivalents and distribution of fragment sizes in the sample, this may require billions of different unique identifiers.

[00251] This method can be cumbersome and expensive. This invention provides methods and compositions in which a population of polynucleotides in a sample of fragmented genomic DNA is tagged with n different unique identifiers, wherein n is at least 2 and no more than 100,000*z, wherein z is a measure of central tendency (e.g., mean, median, mode) of an expected number of duplicate molecules having the same start and stop positions. In certain embodiments, n is at least any of 2*z, 3*z, 4*z, 5*z, 6*z, 7*z, 8*z, 9*z, 10*z, 11*z, 12*z, 13*z, 14*z, 15*z, 16*z, 17*z, 18*z, 19*z, or 20*z (e.g., lower limit). In other embodiments, n is no greater than100,000*z, 10,000*z, 1000*z or 100*z (e.g., upper limit). Thus, n can range between any combination of these lower and upper limits. In certain embodiments, n is between 5*z and 15*z, between 8*z and 12*z, or about 10*z. For example, a haploid human genome equivalent has about 3 picograms of DNA. A sample of about 1 microgram of DNA contains about 300,000 haploid human genome equivalents. The number n can be between 15 and 45, between 24 and 36 or about 30. Improvements in sequencing can be achieved as long as at least some of the duplicate or cognate polynucleotides bear unique identifiers, that is, bear different tags. However, in certain embodiments, the number of tags used is selected so that there is at least a 95% chance that all duplicate molecules starting at any one position bear unique identifiers. For example, a sample comprising about 10,000 haploid human genome equivalents of cfDNA can be tagged with about 36 unique identifiers. The unique identifiers can comprise six unique DNA barcodes. Attached to both ends of a polynucleotide, 36 possible unique identifiers are produced. Samples tagged in such a way can be those with a range of about 10 ng to any of about 100 ng, about 1 μg, about 10 μg of fragmented polynucleotides, e.g., genomic DNA, e.g. cfDNA.

[00252] Accordingly, this invention also provides compositions of tagged polynucleotides. The polynucleotides can comprise fragmented DNA, e.g. cfDNA. A set of polynucleotides in the

composition that map to a mappable base position in a genome can be non-uniquely tagged, that is, the number of different identifiers can be at least at least 2 and fewer than the number of polynucleotides that map to the mappable base position. A composition of between about 10 ng to about 10 μg (e.g., any of about 10 ng-1 μg, about 10 ng-100 ng, about 100 ng-10 μg, about 100 ng-1 μg, about 1 μg-10 μg) can bear between any of 2, 5, 10, 50 or 100 to any of 100, 1000, 10,000 or 100,000 different identifiers. For example, between 5 and 100 different identifiers can be used to tag the polynucleotides in such a composition.

III. Nucleic Acid Sequencing Platforms

[00253] After extraction and isolation of cell free polynucleotides from bodily fluids, cell free sequences may be sequenced. Often, a sequencing method is classic Sanger sequencing. Sequencing methods may include, but are not limited to: high-throughput sequencing, pyrosequencing, sequencing-by-synthesis, single-molecule sequencing, nanopore sequencing, semiconductor sequencing, sequencing-by-ligation, sequencing-by-hybridization, RNA-Seq (Illumina), Digital Gene Expression (Helicos), Next generation sequencing, Single Molecule Sequencing by Synthesis (SMSS)(Helicos), massively-parallel sequencing, Clonal Single Molecule Array (Solexa), shotgun sequencing, Maxim-Gilbert sequencing, primer walking, sequencing using PacBio, SOLiD, Ion Torrent, or Nanopore platforms and any other sequencing methods known in the art.

[00254] In some cases, sequencing reactions various types, as described herein, may comprise a variety of sample processing units. Sample processing units may include but are not limited to multiple lanes, multiple channels, multiple wells, or other mean of processing multiple sample sets substantially simultaneously. Additionally, the sample processing unit may include multiple sample chambers to enable processing of multiple runs simultaneously.

[00255] In some examples, simultaneous sequencing reactions may be performed using multiplex sequencing. In some cases, cell free polynucleotides may be sequenced with at least 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 50000, 100,000 sequencing reactions. In other cases cell free poly nucleotides may be sequenced with less than 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 50000, 100,000 sequencing reactions. Sequencing reactions may be performed sequentially or simultaneously. Subsequent data analysis may be performed on all or part of the sequencing reactions. In some cases, data analysis may be performed on at least 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 50000, 100,000 sequencing reactions. In other

cases data analysis may be performed on less than 1000, 2000, 3000, 4000, 5000, 6000, 7000, 8000, 9000, 10000, 50000, 100,000 sequencing reactions.

[00256] In other examples, the number of sequence reactions may provide coverage for different amounts of the genome. In some cases, sequence coverage of the genome may be at least 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, 99.9% or 100%. In other cases, sequence coverage of the genome may be less than 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, 99.9% or 100%.

[00257] In some examples, sequencing can be performed on cell free polynucleotides that may comprise a variety of different types of nucleic acids. Nucleic acids may be polynucleotides or oligonucleotides. Nucleic acids included, but are not limited to DNA or RNA, single stranded or double stranded or a RNA/cDNA pair.

IV. Polynucleotide Analysis Strategy

[00258] Fig 8. is a diagram, **800**, showing a strategy for analyzing polynucleotides in a sample of initial genetic material. In step **802,** a sample containing initial genetic material is provided. The sample can include target nucleic acid in low abundance. For example, nucleic acid from a normal or wild-type genome (e.g., a germline genome) can predominate in a sample that also includes no more than 20%, no more than 10%, no more than 5%, no more than 1%, no more than 0.5% or no more than 0.1% nucleic acid from at least one other genome containing genetic variation, e.g., a cancer genome or a fetal genome, or a genome from another species. The sample can include, for example, cell free nucleic acid or cells comprising nucleic acid. The initial genetic material can constitute no more than 100 ng nucleic acid. This can contribute to proper oversampling of the original polynucleotides by the sequencing or genetic analysis process. Alternatively, the sample can be artificially capped or bottlenecked to reduce the amount of nucleic acid to no more than 100 ng or selectively enriched to analyze only sequences of interest. The sample can be modified to selectively produce sequence reads of molecules mapping to each of one or more selected locations in a reference sequence. A sample of 100 ng of nucleic acid can contain about 30,000 human haploid genome equivalents, that is, molecules that, together, provide 30,000-fold coverage of a human genome.

[00259] In step **804** the initial genetic material is converted into a set of tagged parent polynucleotides. Tagging can include attaching sequenced tags to molecules in the initial genetic material. Sequenced tags can be selected so that all unique polynucleotides mapping to the same

location in a reference sequence had a unique identifying tag. Conversion can be performed at high efficiency, for example at least 50%.

[00260] In step **806**, the set of tagged parent polynucleotides is amplified to produce a set of amplified progeny polynucleotides. Amplification may be, for example, 1,000-fold.

[00261] In step **808**, the set of amplified progeny polynucleotides are sampled for sequencing. The sampling rate is chosen so that the sequence reads produced both (1) cover a target number of unique molecules in the set of tagged parent polynucleotides and (2) cover unique molecules in the set of tagged parent polynucleotides at a target coverage fold (e.g., 5- to 10-fold coverage of parent polynucleotides.

[00262] In step **810**, the set of sequence reads is collapsed to produce a set of consensus sequences corresponding to unique tagged parent polynucleotides. Sequence reads can be qualified for inclusion in the analysis. For example, sequence reads that fail to meet a quality control scores can be removed from the pool. Sequence reads can be sorted into families representing reads of progeny molecules derived from a particular unique parent molecule. For example, a family of amplified progeny polynucleotides can constitute those amplified molecules derived from a single parent polynucleotide. By comparing sequences of progeny in a family, a consensus sequence of the original parent polynucleotide can be deduced. This produces a set of consensus sequences representing unique parent polynucleotides in the tagged pool.

[00263] In step **812**, the set of consensus sequences is analyzed using any of the analytical methods described herein. For example, consensus sequences mapping to a particular reference sequence location can be analyzed to detect instances of genetic variation. Consensus sequences mapping to particular reference sequences can be measured and normalized against control samples. Measures of molecules mapping to reference sequences can be compared across a genome to identify areas in the genome in which copy number varies, or heterozygosity is lost.

[00264] Fig. 9 is a diagram presenting a more generic method of extracting information from a signal represented by a collection of sequence reads. In this method, after sequencing amplified progeny polynucleotides, the sequence reads are grouped into families of molecules amplified from a molecule of unique identity (910). This grouping can be a jumping off point for methods of interpreting the information in the sequence to determine the contents of the tagged parent polynucleotides with higher fidelity, e.g., less noise and/or distortion.

[00265] Analysis of the collection of sequence reads allows one to make inferences about the parent polynucleotide population from which the sequence reads were generated. Such inferences

may be useful because sequencing typically involves reading only a partial subset of the global total amplified polynucleotides. Therefore, one cannot be certain that every parent polynucleotide will be represented by at least one sequence read in the collection of sequence reads.

[00266] One such inference is the number of unique parent polynucleotides in the original pool. Such an inference can be made based on the number of unique families into which the sequence reads can be grouped and the number of sequence reads in each family. In this case, a family refers to a collection of sequence reads traceable back to an original parent polynucleotide. The inference can be made using well-known statistical methods. For example, if grouping produces many families, each represented by one or a few progeny, then one can infer that the original population included more unique parent polynucleotides that were not sequenced. On the other hand, if grouping produces only a few families, each family represented by many progeny, then one can infer that most of the unique polynucleotides in the parent population are represented by at least one sequence read group into that family.

[00267] Another such inference is the frequency of a base or sequence of bases at a particular locus in an original pool of polynucleotides. Such an inference can be made based on the number of unique families into which the sequence reads can be grouped and the number of sequence reads in each family. Analyzing the base calls at a locus in a family of sequence reads, a confidence score is assigned to each particular base call or sequence. Then, taking into consideration the confidence score for each base call in a plurality of the families, the frequency of each base or sequence at the locus is determined.

V. Copy Number Variation Detection

A. Copy Number Variation Detection Using Single Sample

[00268] Fig 1. is a diagram, **100**, showing a strategy for detection of copy number variation in a single subject. As shown herein, copy number variation detection methods can be implemented as follows. After extraction and isolation of cell free polynucleotides in step **102**, a single unique sample can be sequenced by a nucleic acid sequencing platform known in the art in step **104**. This step generates a plurality of genomic fragment sequence reads. In some cases, these sequences reads may contain barcode information. In other examples, barcodes are not utilized. After sequencing, reads are assigned a quality score. A quality score may be a representation of reads that indicates whether those reads may be useful in subsequent analysis based on a threshold. In some cases, some reads are not of sufficient quality or length to perform the subsequent mapping step. Sequencing

reads with a quality score at least 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data. In other cases, sequencing reads assigned a quality scored less than 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In step **106**, the genomic fragment reads that meet a specified quality score threshold are mapped to a reference genome, or a template sequence that is known not to contain copy number variations. After mapping alignment, sequence reads are assigned a mapping score. A mapping score may be a representation or reads mapped back to the reference sequence indicating whether each position is or is not uniquely mappable. In instances, reads may be sequences unrelated to copy number variation analysis. For example, some sequence reads may originate from contaminant polynucleotides. Sequencing reads with a mapping score at least 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In other cases, sequencing reads assigned a mapping scored less than 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set.

[00269] After data filtering and mapping, the plurality of sequence reads generates a chromosomal region of coverage. In step **108** these chromosomal regions may be divided into variable length windows or bins. A window or bin may be at least 5 kb, 10, kb, 25 kb, 30 kb, 35, kb, 40 kb, 50 kb, 60 kb, 75 kb, 100 kb, 150 kb, 200 kb, 500 kb, or 1000 kb. A window or bin may also have bases up to 5 kb, 10, kb, 25 kb, 30 kb, 35, kb, 40 kb, 50 kb, 60 kb, 75 kb, 100 kb, 150 kb, 200 kb, 500 kb, or 1000 kb. A window or bin may also be about 5 kb, 10, kb, 25 kb, 30 kb, 35, kb, 40 kb, 50 kb, 60 kb, 75 kb, 100 kb, 150 kb, 200 kb, 500 kb, or 1000 kb.

[00270] For coverage normalization in step **110**, each window or bin is selected to contain about the same number of mappable bases. In some cases, each window or bin in a chromosomal region may contain the exact number of mappable bases. In other cases, each window or bin may contain a different number of mappable bases. Additionally, each window or bin may be non-overlapping with an adjacent window or bin. In other cases, a window or bin may overlap with another adjacent window or bin. In some cases a window or bin may overlap by at least 1 bp, 2, bp, 3 bp, 4 bp, 5, bp, 10 bp, 20 bp, 25 bp, 50 bp, 100 bp, 200 bp, 250 bp, 500 bp, or 1000 bp. In other cases, a window or bin may overlap by up to 1 bp, 2, bp, 3 bp, 4 bp, 5, bp, 10 bp, 20 bp, 25 bp, 50 bp, 100 bp, 200 bp, 250 bp, 500 bp, or 1000 bp. In some cases a window or bin may overlap by about 1 bp, 2, bp, 3 bp, 4 bp, 5, bp, 10 bp, 20 bp, 25 bp, 50 bp, 100 bp, 200 bp, 250 bp, 500 bp, or 1000 bp.

[00271] In some cases, each of the window regions may be sized so they contain about the same number of uniquely mappable bases. The mappability of each base that comprise a window region is determined and used to generate a mappability file which contains a representation of reads

from the references that are mapped back to the reference for each file. The mappability file contains one row per every position, indicating whether each position is or is not uniquely mappable.

[00272] Additionally, predefined windows, known throughout the genome to be hard to sequence, or contain a substantially high GC bias, may be filtered from the data set. For example, regions known to fall near the centromere of chromosomes (i.e., centromeric DNA) are known to contain highly repetitive sequences that may produce false positive results. These regions may be filtered out. Other regions of the genome, such as regions that contain an unusually high concentration of other highly repetitive sequences such as microsatellite DNA, may be filtered from the data set.

[00273] The number of windows analyzed may also vary. In some cases, at least 10, 20, 30, 40, 50, 100, 200, 500, 1000, 2000, 5,000, 10,000, 20,000, 50,000 or 100,000 windows are analyzed. In other cases, the number of widows analyzed is up to 10, 20, 30, 40, 50, 100, 200, 500, 1000, 2000, 5,000, 10,000, 20,000, 50,000 or 100,000 windows are analyzed.

[00274] For an exemplary genome derived from cell free polynucleotide sequences, the next step comprises determining read coverage for each window region. This may be performed using either reads with barcodes, or without barcodes. In cases without barcodes, the previous mapping steps will provide coverage of different base positions. Sequence reads that have sufficient mapping and quality scores and fall within chromosome windows that are not filtered, may be counted. The number of coverage reads may be assigned a score per each mappable position. In cases involving barcodes, all sequences with the same barcode, physical properties or combination of the two may be collapsed into one read, as they are all derived from the sample parent molecule. This step reduces biases which may have been introduced during any of the preceding steps, such as steps involving amplification. For example, if one molecule is amplified 10 times but another is amplified 1000 times, each molecule is only represented once after collapse thereby negating the effect of uneven amplification. Only reads with unique barcodes may be counted for each mappable position and influence the assigned score.

[00275] Consensus sequences can be generated from families of sequence reads by any method known in the art. Such methods include, for example, linear or non-linear methods of building consensus sequences (such as voting, averaging, statistical, maximum a posteriori or maximum likelihood detection, dynamic programming, Bayesian, hidden Markov or support vector machine methods, etc.) derived from digital communication theory, information theory, or bioinformatics.

[00276] After the sequence read coverage has been determined, a stochastic modeling algorithm is applied to convert the normalized nucleic acid sequence read coverage for each window region to the discrete copy number states. In some cases, this algorithm may comprise one or more of the following: Hidden Markov Model, dynamic programming, support vector machine, Bayesian network, trellis decoding, Viterbi decoding, expectation maximization, Kalman filtering methodologies and neural networks.

[00277] In step **112**, the discrete copy number states of each window region can be utilized to identify copy number variation in the chromosomal regions. In some cases, all adjacent window regions with the same copy number can be merged into a segment to report the presence or absence of copy number variation state. In some cases, various windows can be filtered before they are merged with other segments.

[00278] In step **114**, the copy number variation may be reported as graph, indicating various positions in the genome and a corresponding increase or decrease or maintenance of copy number variation at each respective position. Additionally, copy number variation may be used to report a percentage score indicating how much disease material (or nucleic acids having a copy number variation) exists in the cell free polynucleotide sample.

[00279] One method of determining copy number variation is shown in Fig. 10. In that method, after grouping sequence reads into families generated from a single parent polynucleotide (1010), the families are quantified, for example, by determining the number of families mapping to each of a plurality of different reference sequence locations. CNVs can be determined directly by comparing a quantitative measure of families at each of a plurality of different loci (1016b). Alternatively, one can infer a quantitative measure of families in the population of tagged parent polynucleotides using both a quantitative measure of families and a quantitative measure of family members in each family, e.g., as discussed above. Then, CNV can be determined by comparing the inferred measure of quantity at the plurality of loci. In other embodiments, a hybrid approach can be taken whereby a similar inference of original quantity can be made following normalization for representational bias during the sequencing process, such as GC bias, etc

B. Copy Number Variation Detection Using Paired Sample

[00280] Paired sample copy number variation detection shares many of the steps and parameters as the single sample approach described herein. However, as depicted in **200** of Fig. 2 of copy number variation detection using paired samples requires comparison of sequence coverage to a

control sample rather than comparing it the predicted mappability of the genome. This approach may aid in normalization across windows.

[00281] Fig 2. is a diagram, **200** showing a strategy for detection of copy number variation in paired subject. As shown herein, copy number variation detection methods can be implemented as follows. In step **204**, a single unique sample can be sequenced by a nucleic acid sequencing platform known in the art after extraction and isolation of the sample in step **202**. This step generates a plurality of genomic fragment sequence reads. Additionally, a sample or control sample is taken from another subject. In some cases, the control subject may be a subject not known to have disease, whereas the other subject may have or be at risk for a particular disease. In some cases, these sequences reads may contain barcode information. In other examples, barcodes are not utilized. After sequencing, reads are assigned a quality score. In some cases, some reads are not of sufficient quality or length to perform the subsequent mapping step. Sequencing reads with a quality score at least 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In other cases, sequencing reads assigned a quality scored less than 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In step **206**, the genomic fragment reads that meet a specified quality score threshold are mapped to a reference genome, or a template sequence that is known not to contain copy number variations. After mapping alignment, sequence reads are assigned a mapping score. In instances, reads may be sequences unrelated to copy number variation analysis. For example, some sequence reads may originate from contaminant polynucleotides. Sequencing reads with a mapping score at least 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In other cases, sequencing reads assigned a mapping scored less than 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set.

[00282] After data filtering and mapping, the plurality of sequence reads generates a chromosomal region of coverage for each of the test and control subjects. In step **208** these chromosomal regions may be divided into variable length windows or bins. A window or bin may be at least 5 kb, 10, kb, 25 kb, 30 kb, 35, kb, 40 kb, 50 kb, 60 kb, 75 kb, 100 kb, 150 kb, 200 kb, 500 kb, or 1000 kb. A window or bin may also be less than 5 kb, 10, kb, 25 kb, 30 kb, 35, kb, 40 kb, 50 kb, 60 kb, 75 kb, 100 kb, 150 kb, 200 kb, 500 kb, or 1000 kb.

[00283] For coverage normalization in step **210**, each window or bin is selected to contain about the same number of mappable bases for each of the test and control subjects. In some cases, each window or bin in a chromosomal region may contain the exact number of mappable bases. In other cases, each window or bin may contain a different number of mappable bases. Additionally,

each window or bin may be non-overlapping with an adjacent window or bin. In other cases, a window or bin may overlap with another adjacent window or bin. In some cases a window or bin may overlap by at least 1 bp, 2, bp, 3 bp, 4 bp, 5, bp, 10 bp, 20 bp, 25 bp, 50 bp, 100 bp, 200 bp, 250 bp, 500 bp, or 1000 bp. In other cases, a window or bin may overlap by less than 1 bp, 2, bp, 3 bp, 4 bp, 5, bp, 10 bp, 20 bp, 25 bp, 50 bp, 100 bp, 200 bp, 250 bp, 500 bp, or 1000 bp.

[00284] In some cases, each of the window regions is sized so they contain about the same number of uniquely mappable bases for each of the test and control subjects. The mappability of each base that comprise a window region is determined and used to generate a mappability file which contains a representation of reads from the references that are mapped back to the reference for each file. The mappability file contains one row per every position, indicating whether each position is or is not uniquely mappable.

[00285] Additionally, predefined windows, known throughout the genome to be hard to sequence, or contain a substantially high GC bias, are filtered from the data set. For example, regions known to fall near the centromere of chromosomes (i.e., centromeric DNA) are known to contain highly repetitive sequences that may produce false positive results. These regions may be filtered. Other regions of the genome, such as regions that contain an unusually high concentration of other highly repetitive sequences such as microsatellite DNA, may be filtered from the data set.

[00286] The number of windows analyzed may also vary. In some cases, at least 10, 20, 30, 40, 50, 100, 200, 500, 1000, 2000, 5,000, 10,000, 20,000, 50,000 or 100,000 windows are analyzed. In other cases, less than 10, 20, 30, 40, 50, 100, 200, 500, 1000, 2000, 5,000, 10,000, 20,000, 50,000 or 100,000 windows are analyzed.

[00287] For an exemplary genome derived from cell free polynucleotide sequences, the next step comprises determining read coverage for each window region for each of the test and control subjects. This may be performed using either reads with barcodes, or without barcodes. In cases without barcodes, the pervious mapping steps will provide coverage of different base positions. Sequence reads that have sufficient mapping and quality scores and fall within chromosome windows that are not filtered, may be counted. The number of coverage reads may be assigned a score per each mappable position. In cases involving barcodes, all sequences with the same barcode may be collapsed into one read, as they are all derived from the sample parent molecule. This step reduces biases which may have been introduced during any of the preceding steps, such as steps involving amplification. Only reads with unique barcodes may be counted for each mappable position and

influence the assigned score. For this reason, it is important that the barcode ligation step be performed in a manner optimized for producing the lowest amount of bias.

[00288] In determining the nucleic acid read coverage for each window, the coverage of each window can be normalized by the mean coverage of that sample. Using such an approach, it may be desirable to sequence both the test subject and the control under similar conditions. The read coverage for each window may be then expressed as a ratio across similar windows

[00289] Nucleic acid read coverage ratios for each window of the test subject can be determined by dividing the read coverage of each window region of the test sample with read coverage of a corresponding window region of the control ample.

[00290] After the sequence read coverage ratios have been determined, a stochastic modeling algorithm is applied to convert the normalized ratios for each window region into discrete copy number states. In some cases, this algorithm may comprise a Hidden Markov Model. In other cases, the stochastic model may comprise dynamic programming, support vector machine, Bayesian modeling, probabilistic modeling, trellis decoding, Viterbi decoding, expectation maximization, Kalman filtering methodologies, or neural networks.

[00291] In step **212**, the discrete copy number states of each window region can be utilized to identify copy number variation in the chromosomal regions. In some cases, all adjacent window regions with the same copy number can be merged into a segment to report the presence or absence of copy number variation state. In some cases, various windows can be filtered before they are merged with other segments.

[00292] In step **214**, the copy number variation may be reported as graph, indicating various positions in the genome and a corresponding increase or decrease or maintenance of copy number variation at each respective position. Additionally, copy number variation may be used to report a percentage score indicating how much disease material exists in the cell free poly nucleotide sample.

VI. Rare mutation Detection

[00293] Rare mutation detection shares similar features as both copy number variation approaches. However, as depicted in Fig. 3, **300**, rare mutation detection uses comparison of sequence coverage to a control sample or reference sequence rather than comparing it the relative mappability of the genome. This approach may aid in normalization across windows.

[00294] Generally, rare mutation detection may be performed on selectively enriched regions of the genome or transcriptome purified and isolated in step **302**. As described herein, specific

regions, which may include but are not limited to genes, oncogenes, tumor suppressor genes, promoters, regulatory sequence elements, non-coding regions, miRNAs, snRNAs and the like may be selectively amplified from a total population of cell free polynucleotides. This may be performed as herein described. In one example, multiplex sequencing may be used, with or without barcode labels for individual polynucleotide sequences. In other examples, sequencing may be performed using any nucleic acid sequencing platforms known in the art. This step generates a plurality of genomic fragment sequence reads as in step **304**. Additionally, a reference sequence is obtained from a control sample, taken from another subject. In some cases, the control subject may be a subject known to not have known genetic aberrations or disease. In some cases, these sequence reads may contain barcode information. In other examples, barcodes are not utilized. After sequencing, reads are assigned a quality score. A quality score may be a representation of reads that indicates whether those reads may be useful in subsequent analysis based on a threshold. In some cases, some reads are not of sufficient quality or length to perform the subsequent mapping step. Sequencing reads with a quality score at least 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In other cases, sequencing reads assigned a quality scored at least 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In step **306**, the genomic fragment reads that meet a specified quality score threshold are mapped to a reference genome, or a reference sequence that is known not to contain rare mutations. After mapping alignment, sequence reads are assigned a mapping score. A mapping score may be a representation or reads mapped back to the reference sequence indicating whether each position is or is not uniquely mappable. In instances, reads may be sequences unrelated to rare mutation analysis. For example, some sequence reads may originate from contaminant polynucleotides. Sequencing reads with a mapping score at least 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set. In other cases, sequencing reads assigned a mapping scored less than 90%, 95%, 99%, 99.9%, 99.99% or 99.999% may be filtered out of the data set.

[00295] For each mappable base, bases that do not meet the minimum threshold for mappability, or low quality bases, may be replaced by the corresponding bases as found in the reference sequence.

[00296] After data filtering and mapping, variant bases found between the sequence reads obtained from the subject and the reference sequence are analyzed.

[00297] For an exemplary genome derived from cell free polynucleotide sequences, the next step comprises determining read coverage for each mappable base position. This may be performed

using either reads with barcodes, or without barcodes. In cases without barcodes, the previous mapping steps will provide coverage of different base positions. Sequence reads that have sufficient mapping and quality scores may be counted. The number of coverage reads may be assigned a score per each mappable position. In cases involving barcodes, all sequences with the same barcode may be collapsed into one consensus read, as they are all derived from the sample parent molecule. The sequence for each base is aligned as the most dominant nucleotide read for that specific location. Further, the number of unique molecules can be counted at each position to derive simultaneous quantification at each position. This step reduces biases which may have been introduced during any of the preceding steps, such as steps involving amplification. Only reads with unique barcodes may be counted for each mappable position and influence the assigned score.

[00298] Once read coverage may be ascertained and variant bases relative to the control sequence in each read are identified, the frequency of variant bases may be calculated as the number of reads containing the variant divided by the total number of reads. This may be expressed as a ratio for each mappable position in the genome.

[00299] For each base position, the frequencies of all four nucleotides, cytosine, guanine, thymine, adenine are analyzed in comparison to the reference sequence. A stochastic or statistical modeling algorithm is applied to convert the normalized ratios for each mappable position to reflect frequency states for each base variant. In some cases, this algorithm may comprise one or more of the following: Hidden Markov Model, dynamic programming, support vector machine, Bayesian or probabilistic modeling, trellis decoding, Viterbi decoding, expectation maximization, Kalman filtering methodologies, and neural networks.

[00300] In step **312**, the discrete rare mutation states of each base position can be utilized to identify a base variant with high frequency of variance as compared to the baseline of the reference sequence. In some cases, the baseline might represent a frequency of at least 0.0001%, 0.001%, 0.01%, 0.1%, 1.0%, 2.0%, 3.0%, 4.0% 5.0%, 10%, or 25%. In other cases the baseline might represent a frequency of at least 0.0001%, 0.001%, 0.01%, 0.1%, 1.0%, 2.0%, 3.0%, 4.0% 5.0%. 10%, or 25%. In some cases, all adjacent base positions with the base variant or mutation can be merged into a segment to report the presence or absence of a rare mutation. In some cases, various positions can be filtered before they are merged with other segments.

[00301] After calculation of frequencies of variance for each base position, the variant with largest deviation for a specific position in the sequence derived from the subject as compared to the

reference sequence is identified as a rare mutation. In some cases, a rare mutation may be a cancer mutation. In other cases, a rare mutation might be correlated with a disease state.

[00302] A rare mutation or variant may comprise a genetic aberration that includes, but is not limited to a single base substitution, or small indels, transversions, translocations, inversion, deletions, truncations or gene truncations. In some cases, a rare mutation may be at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15 or 20 nucleotides in length. On other cases a rare mutation may be at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15 or 20 nucleotides in length.

[00303] In step **314**, the presence or absence of a mutation may be reflected in graphical form, indicating various positions in the genome and a corresponding increase or decrease or maintenance of a frequency of mutation at each respective position. Additionally, rare mutations may be used to report a percentage score indicating how much disease material exists in the cell free polynucleotide sample. A confidence score may accompany each detected mutation, given known statistics of typical variances at reported positions in non-disease reference sequences. Mutations may also be ranked in order of abundance in the subject or ranked by clinically actionable importance.

[00304] Fig. 11 shows a method of inferring the frequency of a base or sequence of bases at a particular locus in a population polynucleotides. Sequence reads are grouped into families generated from an original tagged polynucleotide (1110). For each family, one or more bases at the locus is each assigned a confidence score. The confidence score can be assigned by any of a number of known statistical methods is assigned and can be based, at least in part, on the frequency at which a base appears among the sequence reads belonging to the family (1112). For example, the confidence score can be the frequency at which the base appears among the sequence reads. As another example, for each family, a hidden Markov model can be built, such that a maximum likelihood or maximum a posteriori decision can be made based on the frequency of occurrence of a particular base in a single family. As part of this model, the probability of error and resultant confidence score for a particular decision can be output as well. A frequency of the base in the original population can then be assigned based on the confidence scores among the families (1114).

VII. Applications

A. Early Detection of Cancer

[00305] Numerous cancers may be detected using the methods and systems described herein. Cancers cells, as most cells, can be characterized by a rate of turnover, in which old cells die and replaced by newer cells. Generally dead cells, in contact with vasculature in a given subject, may

release DNA or fragments of DNA into the blood stream. This is also true of cancer cells during various stages of the disease. Cancer cells may also be characterized, dependent on the stage of the disease, by various genetic aberrations such as copy number variation as well as rare mutations. This phenomenon may be used to detect the presence or absence of cancers individuals using the methods and systems described herein.

[00306] For example, blood from subjects at risk for cancer may be drawn and prepared as described herein to generate a population of cell free polynucleotides. In one example, this might be cell free DNA. The systems and methods of the disclosure may be employed to detect rare mutations or copy number variations that may exist in certain cancers present. The method may help detect the presence of cancerous cells in the body, despite the absence of symptoms or other hallmarks of disease.

[00307] The types and number of cancers that may be detected may include but are not limited to blood cancers, brain cancers, lung cancers, skin cancers, nose cancers, throat cancers, liver cancers, bone cancers, lymphomas, pancreatic cancers, skin cancers, bowel cancers, rectal cancers, thyroid cancers, bladder cancers, kidney cancers, mouth cancers, stomach cancers, solid state tumors, heterogeneous tumors, homogenous tumors and the like.

[00308] In the early detection of cancers, any of the systems or methods herein described, including rare mutation detection or copy number variation detection may be utilized to detect cancers. These system and methods may be used to detect any number of genetic aberrations that may cause or result from cancers. These may include but are not limited to mutations, rare mutations, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection and cancer..

[00309] Additionally, the systems and methods described herein may also be used to help characterize certain cancers. Genetic data produced from the system and methods of this disclosure may allow practitioners to help better characterize a specific form of cancer. Often times, cancers are heterogeneous in both composition and staging. Genetic profile data may allow characterization of specific sub-types of cancer that may be important in the diagnosis or treatment of that specific sub-

type. This information may also provide a subject or practitioner clues regarding the prognosis of a specific type of cancer.

B. Cancer Monitoring and Prognosis

[00310] The systems and methods provided herein may be used to monitor already known cancers, or other diseases in a particular subject. This may allow either a subject or practitioner to adapt treatment options in accord with the progress of the disease. In this example, the systems and methods described herein may be used to construct genetic profiles of a particular subject of the course of the disease. In some instances, cancers can progress, becoming more aggressive and genetically unstable. In other examples, cancers may remain benign, inactive, dormant or in remission. The system and methods of this disclosure may be useful in determining disease progression, remission or recurrence.

[00311] Further, the systems and methods described herein may be useful in determining the efficacy of a particular treatment option. In one example, successful treatment options may actually increase the amount of copy number variation or rare mutations detected in subject's blood if the treatment is successful as more cancers may die and shed DNA. In other examples, this may not occur. In another example, perhaps certain treatment options may be correlated with genetic profiles of cancers over time. This correlation may be useful in selecting a therapy. Additionally, if a cancer is observed to be in remission after treatment, the systems and methods described herein may be useful in monitoring residual disease or recurrence of disease.

[00312] For example, mutations occurring within a range of frequency beginning at threshold level can be determined from DNA in a sample from a subject, e.g., a patient. The mutations can be, e.g., cancer related mutations. The frequency can range from, for example, at least 0.1%, at least 1%, or at least 5% to 100%. The sample can be, e.g., cell free DNA or a tumor sample. A course of treatment can be prescribed based on any or all of mutations occurring within the frequency range including, e.g., their frequencies. A sample can be taken from the subject at any subsequent time. Mutations occurring within the original range of frequency or a different range of frequency can be determined. The course of treatment can be adjusted based on the subsequent measurements.

C. Early Detection and Monitoring of Other Diseases or Disease States

[00313] The methods and systems described herein may not be limited to detection of rare mutations and copy number variations associated with only cancers. Various other diseases and infections may result in other types of conditions that may be suitable for early detection and monitoring. For example, in certain cases, genetic disorders or infectious diseases may cause a

certain genetic mosaicism within a subject. This genetic mosaicism may cause copy number variation and rare mutations that could be observed. In another example, the system and methods of the disclosure may also be used to monitor the genomes of immune cells within the body. Immune cells, such as B cells, may undergo rapid clonal expansion upon the presence certain diseases. Clonal expansions may be monitored using copy number variation detection and certain immune states may be monitored. In this example, copy number variation analysis may be performed over time to produce a profile of how a particular disease may be progressing.

[00314] Further, the systems and methods of this disclosure may also be used to monitor systemic infections themselves, as may be caused by a pathogen such as a bacteria or virus. Copy number variation or even rare mutation detection may be used to determine how a population of pathogens are changing during the course of infection. This may be particularly important during chronic infections, such as HIV/AIDs or Hepatitis infections, whereby viruses may change life cycle state and/or mutate into more virulent forms during the course of infection.

[00315] Yet another example that the system and methods of this disclosure may be used for is the monitoring of transplant subjects. Generally, transplanted tissue undergoes a certain degree of rejection by the body upon transplantation. The methods of this disclosure may be used to determine or profile rejection activities of the host body, as immune cells attempt to destroy transplanted tissue. This may be useful in monitoring the status of transplanted tissue as well as altering the course of treatment or prevention of rejection.

[00316] Further, the methods of the disclosure may be used to characterize the heterogeneity of an abnormal condition in a subject, the method comprising generating a genetic profile of extracellular polynucleotides in the subject, wherein the genetic profile comprises a plurality of data resulting from copy number variation and rare mutation analyses. In some cases, including but not limited to cancer, a disease may be heterogeneous. Disease cells may not be identical. In the example of cancer, some tumors are known to comprise different types of tumor cells, some cells in different stages of the cancer. In other examples, heterogeneity may comprise multiple foci of disease. Again, in the example of cancer, there may be multiple tumor foci, perhaps where one or more foci are the result of metastases that have spread from a primary site.

[00317] The methods of this disclosure may be used to generate or profile, fingerprint or set of data that is a summation of genetic information derived from different cells in a heterogeneous disease. This set of data may comprise copy number variation and rare mutation analyses alone or in combination.

D. Early Detection and Monitoring of Other Diseases or Disease States of Fetal Origin

[00318] Additionally, the systems and methods of the disclosure may be used to diagnose, prognose, monitor or observe cancers or other diseases of fetal origin. That is, these methodologies may be employed in a pregnant subject to diagnose, prognose, monitor or observe cancers or other diseases in a unborn subject whose DNA and other polynucleotides may co-circulate with maternal molecules.

VIII. Terminology

[00319] The terminology used therein is for the purpose of describing particular embodiments only and is not intended to be limiting of a systems and methods of this disclosure. As used herein, the singular forms "a", "an" and "the" are intended to include the plural forms as well, unless the context clearly indicates otherwise. Furthermore, to the extent that the terms "including", "includes", "having", "has", "with", or variants thereof are used in either the detailed description and/or the claims, such terms are intended to be inclusive in a manner similar to the term "comprising".

[00320] Several aspects of a systems and methods of this disclosure are described above with reference to example applications for illustration. It should be understood that numerous specific details, relationships, and methods are set forth to provide a full understanding of a systems and methods. One having ordinary skill in the relevant art, however, will readily recognize that a systems and methods can be practiced without one or more of the specific details or with other methods. This disclosure is not limited by the illustrated ordering of acts or events, as some acts may occur in different orders and/or concurrently with other acts or events. Furthermore, not all illustrated acts or events are required to implement a methodology in accordance with this disclosure.

[00321] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another embodiment. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. The term "about" as used herein refers to a range that is 15% plus or minus from a stated numerical value within the context of the particular usage. For example, about 10 would include a range from 8.5 to 11.5.

Computer systems

[00322] Methods of the present disclosure can be implemented using, or with the aid of, computer systems. FIG. 15 shows a computer system 1501 that is programmed or otherwise configured to implement the methods of the present disclosure. The computer system 1501 can regulate various aspects sample preparation, sequencing and/or analysis. In some examples, the computer system 1501 is configured to perform sample preparation and sample analysis, including nucleic acid sequencing.

[00323] The computer system 1501 includes a central processing unit (CPU, also "processor" and "computer processor" herein) 1505, which can be a single core or multi core processor, or a plurality of processors for parallel processing. The computer system 1501 also includes memory or memory location 1510 (e.g., random-access memory, read-only memory, flash memory), electronic storage unit 1515 (e.g., hard disk), communication interface 1520 (e.g., network adapter) for communicating with one or more other systems, and peripheral devices 1525, such as cache, other memory, data storage and/or electronic display adapters. The memory 1510, storage unit 1515, interface 1520 and peripheral devices 1525 are in communication with the CPU 1505 through a communication bus (solid lines), such as a motherboard. The storage unit 1515 can be a data storage unit (or data repository) for storing data. The computer system 1501 can be operatively coupled to a computer network ("network") 1530 with the aid of the communication interface 1520. The network 1530 can be the Internet, an internet and/or extranet, or an intranet and/or extranet that is in communication with the Internet. The network 1530 in some cases is a telecommunication and/or data network. The network 1530 can include one or more computer servers, which can enable distributed computing, such as cloud computing. The network 1530, in some cases with the aid of the computer system 1501, can implement a peer-to-peer network, which may enable devices coupled to the computer system 1501 to behave as a client or a server.

[00324] The CPU 1505 can execute a sequence of machine-readable instructions, which can be embodied in a program or software. The instructions may be stored in a memory location, such as the memory 1510. Examples of operations performed by the CPU 1505 can include fetch, decode, execute, and writeback.

[00325] The storage unit 1515 can store files, such as drivers, libraries and saved programs. The storage unit 1515 can store programs generated by users and recorded sessions, as well as output(s) associated with the programs. The storage unit 1515 can store user data, e.g., user preferences and user programs. The computer system 1501 in some cases can include one or more additional data storage units that are external to the computer system 1501, such as located on a

remote server that is in communication with the computer system 1501 through an intranet or the Internet.

[00326] The computer system 1501 can communicate with one or more remote computer systems through the network 1530. For instance, the computer system 1501 can communicate with a remote computer system of a user (e.g., operator). Examples of remote computer systems include personal computers (e.g., portable PC), slate or tablet PC's (e.g., Apple® iPad, Samsung® Galaxy Tab), telephones, Smart phones (e.g., Apple® iPhone, Android-enabled device, Blackberry®), or personal digital assistants. The user can access the computer system 1501 via the network 1530.

[00327] Methods as described herein can be implemented by way of machine (e.g., computer processor) executable code stored on an electronic storage location of the computer system 1501, such as, for example, on the memory 1510 or electronic storage unit 1515. The machine executable or machine readable code can be provided in the form of software. During use, the code can be executed by the processor 1505. In some cases, the code can be retrieved from the storage unit 1515 and stored on the memory 1510 for ready access by the processor 1505. In some situations, the electronic storage unit 1515 can be precluded, and machine-executable instructions are stored on memory 1510.

[00328] The code can be pre-compiled and configured for use with a machine have a processer adapted to execute the code, or can be compiled during runtime. The code can be supplied in a programming language that can be selected to enable the code to execute in a pre-compiled or as-compiled fashion.

[00329] Aspects of the systems and methods provided herein, such as the computer system 1501, can be embodied in programming. Various aspects of the technology may be thought of as "products" or "articles of manufacture" typically in the form of machine (or processor) executable code and/or associated data that is carried on or embodied in a type of machine readable medium. Machine-executable code can be stored on an electronic storage unit, such memory (e.g., read-only memory, random-access memory, flash memory) or a hard disk. "Storage" type media can include any or all of the tangible memory of the computers, processors or the like, or associated modules thereof, such as various semiconductor memories, tape drives, disk drives and the like, which may provide non-transitory storage at any time for the software programming. All or portions of the software may at times be communicated through the Internet or various other telecommunication networks. Such communications, for example, may enable loading of the software from one computer or processor into another, for example, from a management server or host computer into the

computer platform of an application server. Thus, another type of media that may bear the software elements includes optical, electrical and electromagnetic waves, such as used across physical interfaces between local devices, through wired and optical landline networks and over various air-links. The physical elements that carry such waves, such as wired or wireless links, optical links or the like, also may be considered as media bearing the software. As used herein, unless restricted to non-transitory, tangible "storage" media, terms such as computer or machine "readable medium" refer to any medium that participates in providing instructions to a processor for execution.

[00330] Hence, a machine readable medium, such as computer-executable code, may take many forms, including but not limited to, a tangible storage medium, a carrier wave medium or physical transmission medium. Non-volatile storage media include, for example, optical or magnetic disks, such as any of the storage devices in any computer(s) or the like, such as may be used to implement the databases, etc. shown in the drawings. Volatile storage media include dynamic memory, such as main memory of such a computer platform. Tangible transmission media include coaxial cables; copper wire and fiber optics, including the wires that comprise a bus within a computer system. Carrier-wave transmission media may take the form of electric or electromagnetic signals, or acoustic or light waves such as those generated during radio frequency (RF) and infrared (IR) data communications. Common forms of computer-readable media therefore include for example: a floppy disk, a flexible disk, hard disk, magnetic tape, any other magnetic medium, a CD-ROM, DVD or DVD-ROM, any other optical medium, punch cards paper tape, any other physical storage medium with patterns of holes, a RAM, a ROM, a PROM and EPROM, a FLASH-EPROM, any other memory chip or cartridge, a carrier wave transporting data or instructions, cables or links transporting such a carrier wave, or any other medium from which a computer may read programming code and/or data. Many of these forms of computer readable media may be involved in carrying one or more sequences of one or more instructions to a processor for execution.

[00331] The computer system 1501 can include or be in communication with an electronic display that comprises a user interface (UI) for providing, for example, one or more results of sample analysis. Examples of UI's include, without limitation, a graphical user interface (GUI) and web-based user interface.

EXAMPLES

Example 1 – Prostate Cancer Prognosis and Treatment

[00332] A blood sample is taken from a prostate cancer subject. Previously, an oncologist determines that the subject has stage II prostate cancer and recommends a treatment. Cell free DNA is extracted, isolated, sequenced and analyzed every 6 months after the initial diagnosis.

[00333] Cell free DNA is extracted and isolated from blood using the Qiagen Qubit kit protocol. A carrier DNA is added to increase yields. DNA is amplified using PCR and universal primers. 10 ng of DNA is sequenced using a massively parallel sequencing approach with an Illumina MiSeq personal sequencer. 90% of the subject's genome is covered through sequencing of cell free DNA.

[00334] Sequence data is assembled and analyzed for copy number variation. Sequence reads are mapped and compared to a healthy individual (control). Based on the number of sequence reads, chromosomal regions are divided into 50 kb non overlapping regions. Sequence reads are compared to one another and a ratio is determined for each mappable position.

[00335] A Hidden Markov Model is applied to convert copy numbers into discrete states for each window.

[00336] Reports are generated, mapping genome positions and copy number variation show in Fig. 4A (for a healthy individual) and Fig. 4B for the subject with cancer.

[00337] These reports, in comparison to other profiles of subjects with known outcomes, indicate that this particular cancer is aggressive and resistant to treatment. The cell free tumor burden is 21%. The subject is monitored for 18 months. At month 18, the copy number variation profile begins to increase dramatically, from cell free tumor burden of 21% to 30%. A comparison is done with genetic profiles of other prostate subjects. It is determined that this increase in copy number variation indicates that the prostate cancer is advancing from stage II to stage III. The original treatment regiment as prescribed is no longer treating the cancer. A new treatment is prescribed.

[00338] Further, these reports are submitted and accessed electronically via the internet. Analysis of sequence data occurs at a site other than the location of the subject. The report is generated and transmitted to the subject's location. Via an internet enabled computer, the subject accesses the reports reflecting his tumor burden (Fig. 4C).

Example 2 – Prostate Cancer Remission and Recurrence.

[00339] A blood sample is taken from a prostate cancer survivor. The subject had previously undergone numerous rounds of chemotherapy and radiation. The subject at the time of testing did not

present symptoms or health issues related to the cancer. Standard scans and assays reveal the subject to be cancer free.

[00340] Cell free DNA is extracted and isolated from blood using the Qiagen TruSeq kit protocol. A carrier DNA is added to increase yields. DNA is amplified using PCR and universal primers. 10 ng of DNA is sequenced using a massively parallel sequencing approach with an Illumina MiSeq personal sequencer. 12mer barcodes are added to individual molecules using a ligation method.

[00341] Sequence data is assembled and analyzed for copy number variation. Sequence reads are mapped and compared to a healthy individual (control). Based on the number of sequence reads, chromosomal regions are divided into 40 kb non overlapping regions. Sequence reads are compared to one another and a ratio is determined for each mappable position.

[00342] Non unique barcoded sequences are collapsed into a single read to help normalize bias from amplification.

[00343] A Hidden Markov Model is applied to convert copy numbers into discrete states for each window.

[00344] Reports are generated, mapping genome positions and copy number variation shown in Fig. 5A, for a subject with cancer in remission and Fig. 5B for a subject with cancer in recurrence.

[00345] This report in comparison to other profiles of subjects with known outcomes indicates that at month 18, rare mutation analysis for copy number variation is detected at cell free tumor burden of 5%. An oncologist prescribes treatment again.

Example 3 – Thyroid Cancer and Treatment

[00346] A subject is known to have Stage IV thyroid cancer and undergoes standard treatment, including radiation therapy with I-131. CT scans are inconclusive as to whether the radiation therapy is destroying cancerous masses. Blood is drawn before and after the latest radiation session.

[00347] Cell free DNA is extracted and isolated from blood using the Qiagen Qubit kit protocol. A sample of non specific bulk DNA is added to the sample preparation reactions increase yields.

[00348] It is known that the BRAF gene may be mutated at amino acid position 600 in this thyroid cancer. From population of cell free DNA, BRAF DNA is selectively amplified using primers specific to the gene. 20mer barcodes are added to the parent molecule as a control for counting reads.

[00349] 10 ng of DNA is sequenced using massively parallel sequencing approach with an Illumina MiSeq personal sequencer.

[00350] Sequence data is assembled and analyzed for copy number variation detection. Sequence reads are mapped and compared to a healthy individual (control). Based on the number of sequence reads, as determined by counting the barcode sequences, chromosomal regions are divided into 50 kb non overlapping regions. Sequence reads are compared to one another and a ratio is determined for each mappable position.

[00351] A Hidden Markov Model is applied to convert copy numbers into discrete states for each window.

[00352] A report is generated, mapping genome positions and copy number variation.

[00353] The reports generated before and after treatment are compared. The tumor cell burden percentage jumps from 30% to 60% after the radiation session. The jump in tumor burden is determined to be an increase in necrosis of cancer tissue versus normal tissue as a result of treatment. Oncologists recommend the subject continue the prescribed treatment.

Example 4 – Sensitivity of Rare mutation Detection

[00354] In order to determine the detection ranges of rare mutation present in a population of DNA, mixing experiments are performed. Sequences of DNA, some containing wildtype copies of the genes TP53, HRAS and MET and some containing copies with rare mutations in the same genes, are mixed together in distinct ratios. DNA mixtures are prepared such that ratios or percentages of mutant DNA to wildtype DNA range from 100% to 0.01%.

[00355] 10 ng of DNA is sequenced for each mixing experiment using a massively parallel sequencing approach with an Illumina MiSeq personal sequencer.

[00356] Sequence data is assembled and analyzed for rare mutation detection. Sequence reads are mapped and compared to a reference sequence (control). Based on the number of sequence reads, the frequency of variance for each mappable position is determined.

[00357] A Hidden Markov Model is applied to convert frequency of variance for each mappable position into discrete states for base position.

[00358] A report is generated, mapping genome base positions and percentage detection of the rare mutation over baseline as determined by the reference sequence (Fig. 6A).

[00359] The results of various mixing experiments ranging from 0.1% to 100% are represented in a logarithmic scale graph, with measured percentage of DNA with a rare mutation

graphed as a function of the actual percentage of DNA with a rare mutation (Fig. 6B). The three genes, TP53, HRAS and MET are represented. A strong linear correlation is found between measured and expected rare mutation populations. Additionally, a lower sensitivity threshold of about 0.1% of DNA with a rare mutation in a population of non mutated DNA is found with these experiments (Fig. 6B).

Example 5 –Rare mutation Detection in Prostate Cancer Subject

[00360] A subject is thought to have early stage prostate cancer. Other clinical tests provide inconclusive results. Blood is drawn from the subject and cell free DNA is extracted, isolated, prepared and sequenced.

[00361] A panel of various oncogenes and tumor suppressor genes are selected for selective amplification using a TaqMan© PCR kit (Invitrogen) using gene specific primers. DNA regions amplified include DNA containing PIK3CA and TP53 genes.

[00362] 10 ng of DNA is sequenced using a massively parallel sequencing approach with an Illumina MiSeq personal sequencer.

[00363] Sequence data is assembled and analyzed for rare mutation detection. Sequence reads are mapped and compared to a reference sequence (control). Based on the number of sequence reads, the frequency of variance for each mappable position was determined.

[00364] A Hidden Markov Model is applied to convert frequency of variance for each mappable position into discrete states for each base position.

[00365] A report is generated, mapping genomic base positions and percentage detection of the rare mutation over baseline as determined by the reference sequence (Fig. 7A). Rare mutations are found at an incidence of 5% in two genes, PIK3CA and TP53, respectively, indicating that the subject has an early stage cancer. Treatment is initiated.

[00366] Further, these reports are submitted and accessed electronically via the internet. Analysis of sequence data occurs at a site other than the location of the subject. The report is generated and transmitted to the subject's location. Via an internet enabled computer, the subject accesses the reports reflecting his tumor burden (Fig. 7B).

Example 6 –Rare mutation Detection in Colorectal Cancer Subjects

[00367] A subject is thought to have mid-stage colorectal cancer. Other clinical tests provide inconclusive results. Blood is drawn from the subject and cell free DNA is extracted.

[00368] 10 ng of the cell-free genetic material that is extracted from a single tube of plasma is used. The initial genetic material is converted into a set of tagged parent polynucleotides. The tagging included attaching tags required for sequencing as well as non-unique identifiers for tracking progeny molecules to the parent nucleic acids. The conversion is performed through an optimized ligation reaction as described above and conversion yield is confirmed by looking at the size profile of molecules post-ligation. Conversion yield is measured as the percentage of starting initial molecules that have both ends ligated with tags. Conversion using this approach is performed at high efficiency, for example, at least 50%.

[00369] The tagged library is PCR-amplified and enriched for genes most associated with colorectal cancer, (e.g., KRAS, APC, TP53, etc) and the resulting DNA is sequenced using a massively parallel sequencing approach with an Illumina MiSeq personal sequencer.

[00370] Sequence data is assembled and analyzed for rare mutation detection. Sequence reads are collapsed into familial groups belonging to a parent molecule (as well as error-corrected upon collapse) and mapped using a reference sequence (control). Based on the number of sequence reads, the frequency of rare variations (substitutions, insertions, deletions, etc) and variations in copy number and heterozygosity (when appropriate) for each mappable position is determined.

[00371] A report is generated, mapping genomic base positions and percentage detection of the rare mutation over baseline as determined by the reference sequence. Rare mutations are found at an incidence of 0.3-0.4% in two genes, KRAS and FBXW7, respectively, indicating that the subject has residual cancer. Treatment is initiated.

[00372] Further, these reports are submitted and accessed electronically via the internet. Analysis of sequence data occurs at a site other than the location of the subject. The report is generated and transmitted to the subject's location. Via an internet enabled computer, the subject accesses the reports reflecting his tumor burden.

[00373] **Example 7 – Digital Sequencing Technology**

[00374] The concentrations of tumor-shed nucleic acids are typically so low that current next-generation sequencing technologies can only detect such signals sporadically or in patients with terminally high tumor burden. The main reason being that such technologies are plagued by error rates and bias that can be orders of magnitude higher than what is required to reliably detect de novo genetic alterations associated with cancer in circulating DNA. Shown here is a new sequencing methodology, Digital Sequencing Technology (DST), which increases the sensitivity and specificity

of detecting and quantifying rare tumor-derived nucleic acids among germline fragments by at least 1-2 orders of magnitude.

[00375] DST architecture is inspired by state-of-the-art digital communication systems that combat the high noise and distortion caused by modern communication channels and are able to transmit digital information flawlessly at exceedingly high data rates. Similarly, current next-gen workflows are plagued by extremely high noise and distortion (due to sample-prep, PCR-based amplification and sequencing). Digital sequencing is able to eliminate the error and distortion created by these processes and produce near-perfect representation of all rare variants (including CNVs).

[00376] High-Diversity Library preparation

[00377] Unlike conventional sequencing library preparation protocols, whereby the majority of extracted circulating DNA fragments are lost due to inefficient library conversion, our Digital Sequencing Technology workflow enables the vast majority of starting molecules to be converted and sequenced. This is critically important for detection of rare variants as there may only be a handful of somatically mutated molecules in an entire 10mL tube of blood. The efficient molecular biology conversion process developed enables the highest possible sensitivity for detection of rare variants.

[00378] Comprehensive Actionable Oncogene Panel

[00379] The workflow engineered around the DST platform is flexible and highly tunable as targeted regions can be as small as single exons or as broad as whole exomes (or even whole genomes). A standard panel consists of all exonic bases of 15 actionable cancer-related genes and coverage of the "hot" exons of an additional 36 onco-/tumor-suppressor genes (e.g., exons containing at least one or more reported somatic mutations in COSMIC).

[00380] **Example 8: Analytical Studies**

[00381] To study the performance of our technology, its sensitivity in analytical samples was evaluated. We spiked varying amounts of LNCaP cancer cell line DNA into a background of normal cfDNA and were able to successfully detect somatic mutations down to 0.1% sensitivity (see Figure 13).

[00382] Preclinical Studies

[00383] The concordance of circulating DNA with tumor gDNA in human xenograft models in mice was investigated. In seven CTC-negative mice, each with one of two different human breast cancer tumors, all somatic mutations detected in tumor gDNA were also detected in mouse blood cfDNA using DST further validating the utility of cfDNA for non-invasive tumor genetic profiling.

[00384] Pilot Clinical Studies

[00385] Correlation of tumor biopsy vs. circulating DNA somatic mutations

[00386] A pilot study was initiated on human samples across different cancer types. The concordance of tumor mutation profiles derived from circulating cell-free DNA with those derived from matched tumor biopsy samples was investigated. Higher than 93% concordance between tumor and cfDNA somatic mutation profiles in both colorectal and melanoma cancers across 14 patients was found (Table 1).

Table 1

Patient ID	**Stage**	**Mutant Genes in Matched Tumor**	**Percentage of mutant cfDNA**
CRC #1	II-B	TP53	0.2%
CRC #2	II-C	KRAS	0.6%
		SMAD4	1.5%
		GNAS	1.4%
		FBXW7	0.8%
CRC #3	III-B	KRAS	1.1%
		TP53	1.4%
		PIK3CA	1.7%
		APC	0.7%
CRC #4	III-B	KRAS	0.3%
		TP53	0.4%
CRC #5	III-B	KRAS	0.04%
CRC #6	III-C	KRAS	0.03%
CRC #7	IV	PIK3CA	1.3%
		KRAS	0.6%
		TP53	0.8%
CRC #8	IV	APC	0.3%
		SMO	0.6%
		TP53	0.4%

		KRAS	0.0%
CRC #9	IV	APC	47.3%
		APC	40.2%
		KRAS	37.7%
		PTEN	0.0%
		TP53	12.9%
CRC #10	IV	TP53	0.9%
Melanoma #1	IV	BRAF	0.2%
Melanoma #2	IV	APC	0.3%
		EGFR	0.9%
		MYC	10.5%
Melanoma #3	IV	BRAF	3.3%
Melanoma #4	IV	BRAF	0.7%

[00387] It should be understood from the foregoing that, while particular implementations have been illustrated and described, various modifications can be made thereto and are contemplated herein. It is also not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the preferable embodiments herein are not meant to be construed in a limiting sense. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations or relative proportions set forth herein which depend upon a variety of conditions and variables. Various modifications in form and detail of the embodiments of the invention will be apparent to a person skilled in the art. It is therefore contemplated that the invention shall also cover any such modifications, variations and equivalents.

WHAT IS CLAIMED IS:

1. A method for detecting copy number variation comprising:
    a. sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide generate a plurality of sequencing reads;
    b. filtering out reads that fail to meet a set threshold;
    c. mapping the sequence reads obtained from step (a), after reads are filtered out, to a reference sequence;
    d. quantifying or enumerating mapped reads in two or more predefined regions of the reference sequence; and
    e. determining copy number variation in one or more of the predefined regions by:
        i. normalizing number of reads in the predefined regions to each other and/or the number of unique sequence reads in the predefined regions to one another;
        ii. comparing the normalized numbers obtained in step (i) to normalized numbers obtained from a control sample.

2. A method for detecting a rare mutation in a cell-free or substantially cell free sample obtained from a subject comprising:
    a. sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotide generate a plurality of sequencing reads;
    b. performing multiplex sequencing on regions or whole-genome sequencing if enrichment is not performed;
    c. filtering out reads that fail to meet a set threshold;
    d. mapping sequence reads derived from the sequencing onto a reference sequence;
    e. identifying a subset of mapped sequence reads that align with a variant of the reference sequence at each mappable base position;
    f. for each mappable base position, calculating a ratio of (a) a number of mapped sequence reads that include a variant as compared to the reference sequence, to (b) a number of total sequence reads for each mappable base position;

g. normalizing the ratios or frequency of variance for each mappable base position and determining potential rare variant(s) or mutation(s); and
h. and comparing the resulting number for each of the regions with potential rare variant(s) or mutation(s) to similarly derived numbers from a reference sample.

3. A method of characterizing the heterogeneity of an abnormal condition in a subject, the method comprising generating a genetic profile of extracellular polynucleotides in the subject, wherein the genetic profile comprises a plurality of data resulting from copy number variation and rare mutation analyses.

4. The method of claim 1, 2, or 3 wherein the prevalence/concentration of each rare variant identified in the subject is reported and quantified simultaneously.

5. The method of claim 1, 2, or 3 wherein a confidence score, regarding the prevalence/concentrations of rare variants in the subject, is reported.

6. The method of claim 1, 2, or 3 wherein the extracellular polynucleotides comprise DNA.

7. The method of claim 1, 2, or 3 wherein the extracellular polynucleotides comprise RNA.

8. The method of claim 1, 2, or 3 further comprising isolating extracellular polynucleotides from the bodily sample.

9. The method claim 1, 2, or 3 wherein the isolating comprises a method for circulating nucleic acid isolation and extraction.

10. The method of claim 1, 2, or 3 further comprising fragmenting said isolated extracellular polynucleotides.

11. The method of claim 8 wherein the bodily sample is selected from the group consisting of blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool and tears.

12. The method of claim 1, 2, or 3, further comprising the step of determining the percent of sequences having copy number variation or rare mutation or variant in said bodily sample.

13. The method of claim 12 wherein the determining comprises calculating the percentage of predefined regions with an amount of polynucleotides above or below a predetermined threshold.

14. The method of claim 1, 2, or 3 wherein the subject is suspected of having an abnormal condition.

15. The method of claim 14 wherein the abnormal condition is selected from the group consisting of, mutations, rare mutations, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection and cancer.

16. The method of claim 1, 2, or 3 wherein the subject is a pregnant female.

17. The method of claim 1 or 2 wherein the copy number variation or rare mutation or genetic variant is indicative of a fetal abnormality.

18. The method of claim 17 wherein the fetal abnormality is selected from the group consisting of, mutations, rare mutations, indels, copy number variations, transversions, translocations, inversion, deletions, aneuploidy, partial aneuploidy, polyploidy, chromosomal instability, chromosomal structure alterations, gene fusions, chromosome fusions, gene truncations, gene amplification, gene duplications, chromosomal lesions, DNA lesions, abnormal changes in nucleic acid chemical modifications, abnormal changes in epigenetic patterns, abnormal changes in nucleic acid methylation infection and cancer.

19. The method of claim 1, 2, or 3 further comprising attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to sequencing.

20. The method of claim 19 wherein each barcode attached to extracellular polynucleotides or fragments thereof prior to sequencing is unique.

21. The method of claim 19 wherein each barcode attached to extracellular polynucleotides or fragments thereof prior to sequencing is not unique.

22. The method of claim 1, 2, or 3 further comprising selectively enriching regions from the subject's genome or transcriptome prior to sequencing.

23. The method of claim 1, 2, or 3 further comprising non-selectively enriching regions from the subject's genome or transcriptome prior to sequencing.

24. The method of claim 1, 2, or 3 further comprising attaching one or more barcodes to the extracellular polynucleotides or fragments thereof prior to any amplification or enrichment step.

25. The method of claim 19 wherein the barcode is a polynucleotide.

26. The method of claim 19 wherein the barcode comprises random sequence.

27. The method of claim 19 wherein the barcode comprises a fixed or semi-random set of oligonucleotides that in combination with the diversity of molecules sequenced from a select region enables identification of unique molecules.

28. The method of claim 19 wherein the barcodes comprise oligonucleotides is at least a 3, 5, 10, 15, 20 25, 30, 35, 40, 45, or 50mer base pairs in length.

29. The method of claim 1, 2, or 3 further comprises amplifying the extracellular polynucleotides or fragments thereof.

30. The method of claim 29 wherein the amplification comprises global amplification or whole genome amplification.

ABSTRACT OF THE DISCLOSURE

The present disclosure provides a system and method for the detection of rare mutations and copy number variations in cell free polynucleotides. Generally, the systems and methods comprise sample preparation, or the extraction and isolation of cell free polynucleotide sequences from a bodily fluid; subsequent sequencing of cell free polynucleotides by techniques known in the art; and application of bioinformatics tools to detect rare mutations and copy number variations as compared to a reference. The systems and methods also may contain a database or collection of different rare mutations or copy number variation profiles of different diseases, to be used as additional references in aiding detection of rare mutations, copy number variation profiling or general genetic profiling of a disease.

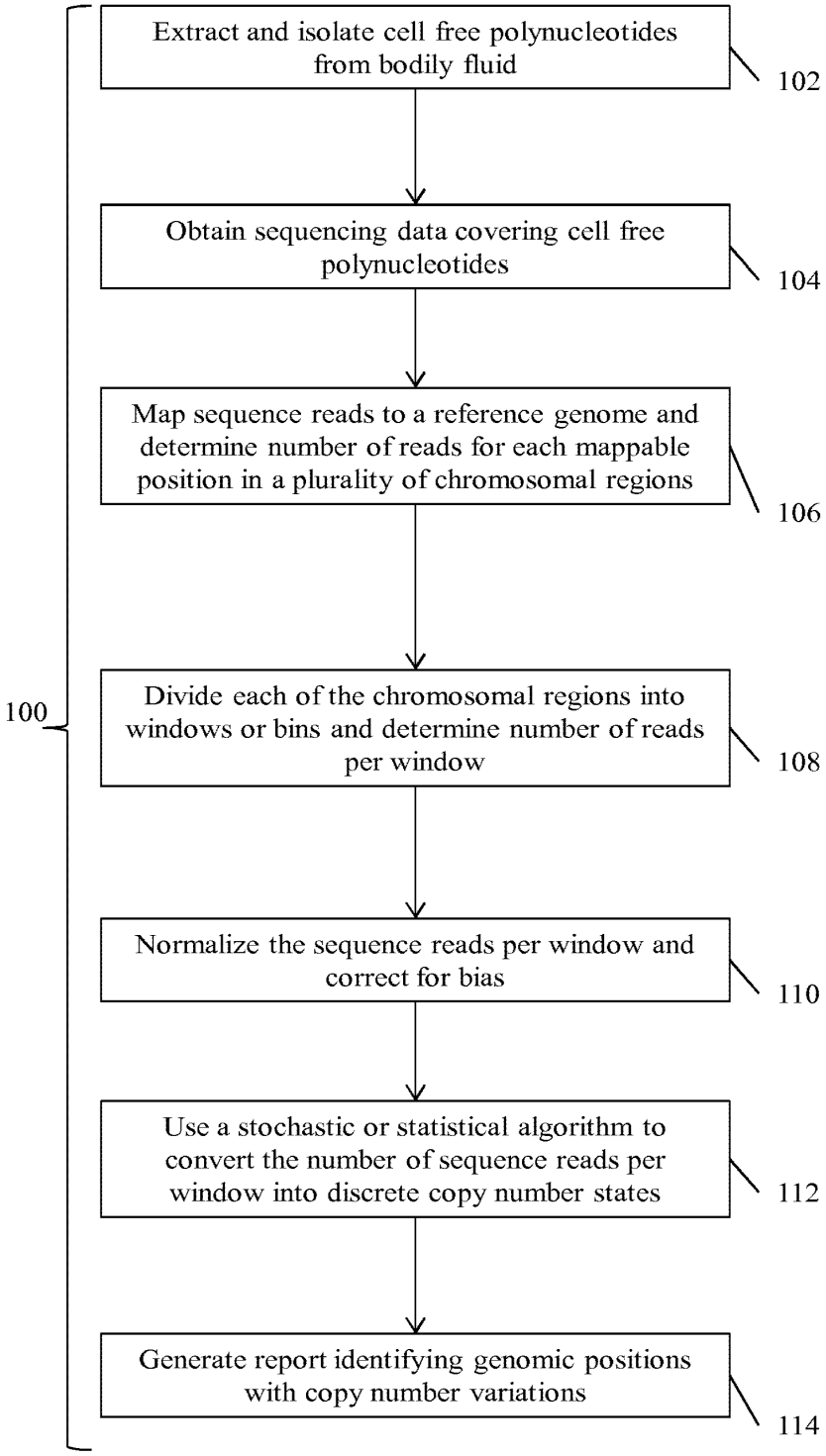

Extract and isolate cell free polynucleotides from bodily fluid
102
Obtain sequencing data covering cell free polynucleotides
104
Map sequence reads to a reference genome and determine number of reads for each mappable position in a plurality of chromosomal regions
106
Divide each of the chromosomal regions into windows or bins and determine number of reads per window
108
Normalize the sequence reads per window and correct for bias
110
Use a stochastic or statistical algorithm to convert the number of sequence reads per window into discrete copy number states
112
Generate report identifying genomic positions with copy number variations
114
100

Fig. 1

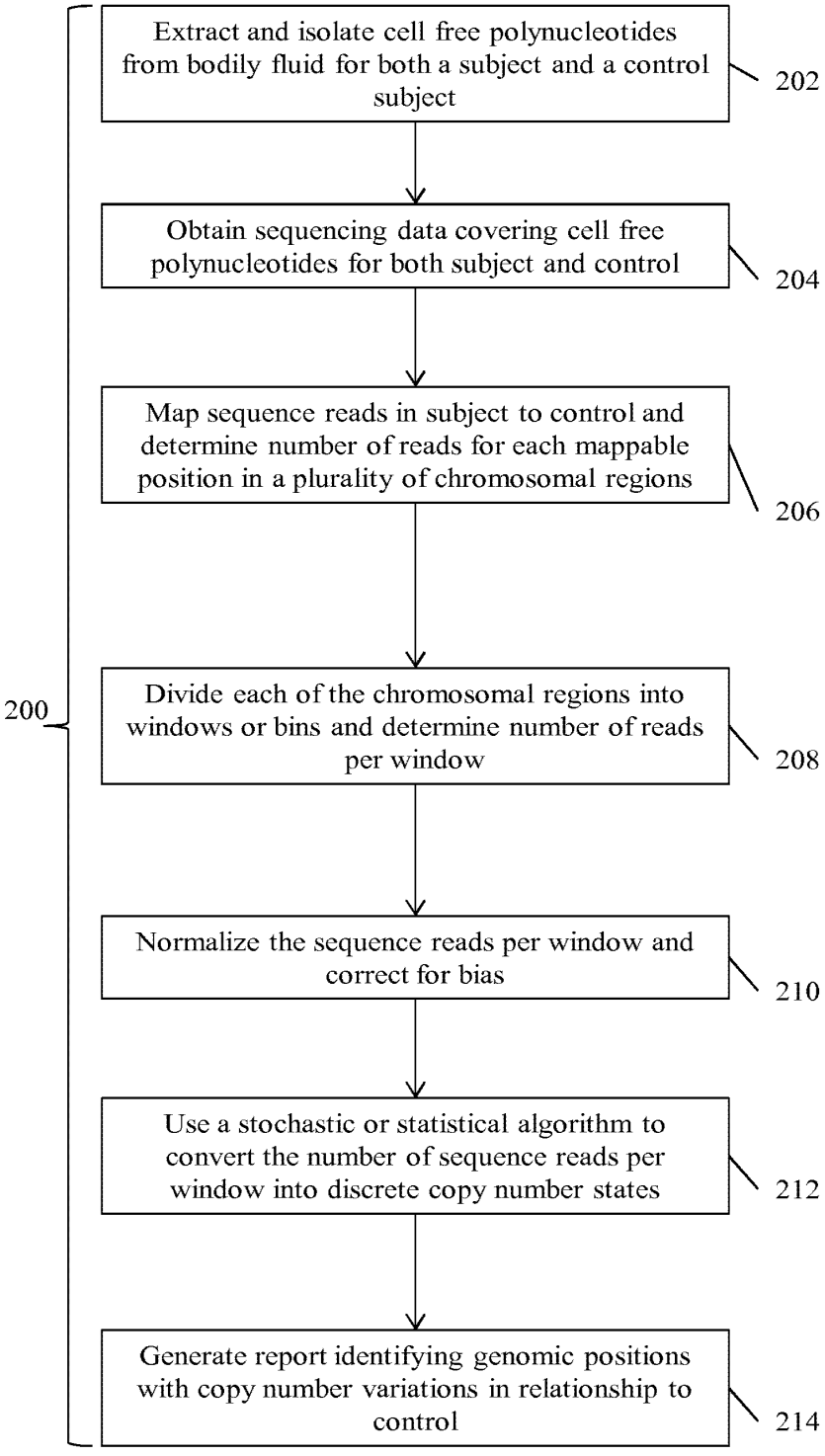

Extract and isolate cell free polynucleotides from bodily fluid for both a subject and a control subject
202
Obtain sequencing data covering cell free polynucleotides for both subject and control
204
Map sequence reads in subject to control and determine number of reads for each mappable position in a plurality of chromosomal regions
206
Divide each of the chromosomal regions into windows or bins and determine number of reads per window
208
Normalize the sequence reads per window and correct for bias
210
Use a stochastic or statistical algorithm to convert the number of sequence reads per window into discrete copy number states
212
Generate report identifying genomic positions with copy number variations in relationship to control
214
200

Fig. 2

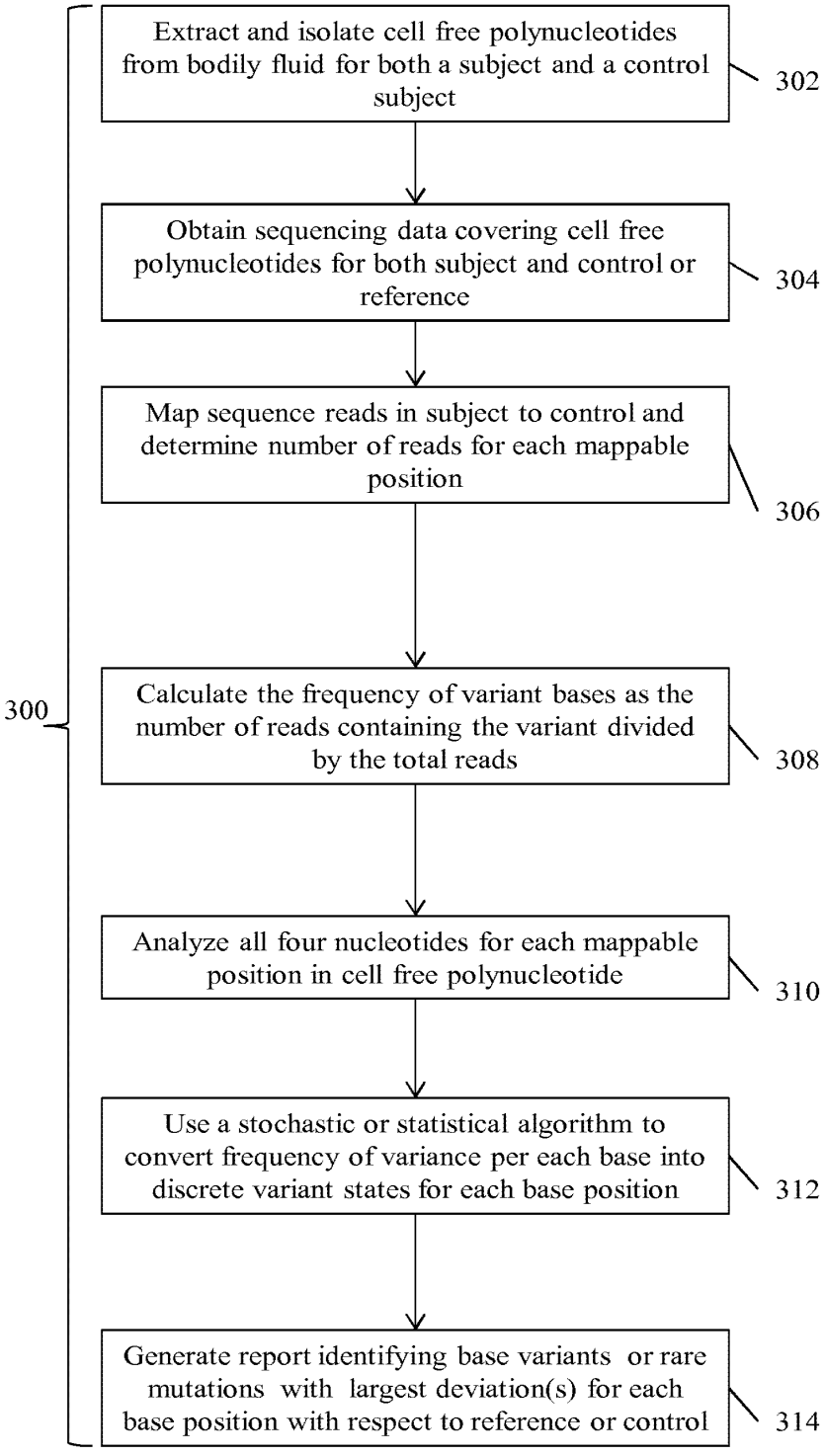

Extract and isolate cell free polynucleotides from bodily fluid for both a subject and a control subject
302
Obtain sequencing data covering cell free polynucleotides for both subject and control or reference
304
Map sequence reads in subject to control and determine number of reads for each mappable position
306
Calculate the frequency of variant bases as the number of reads containing the variant divided by the total reads
308
Analyze all four nucleotides for each mappable position in cell free polynucleotide
310
Use a stochastic or statistical algorithm to convert frequency of variance per each base into discrete variant states for each base position
312
Generate report identifying base variants or rare mutations with largest deviation(s) for each base position with respect to reference or control
314
300

Fig. 3

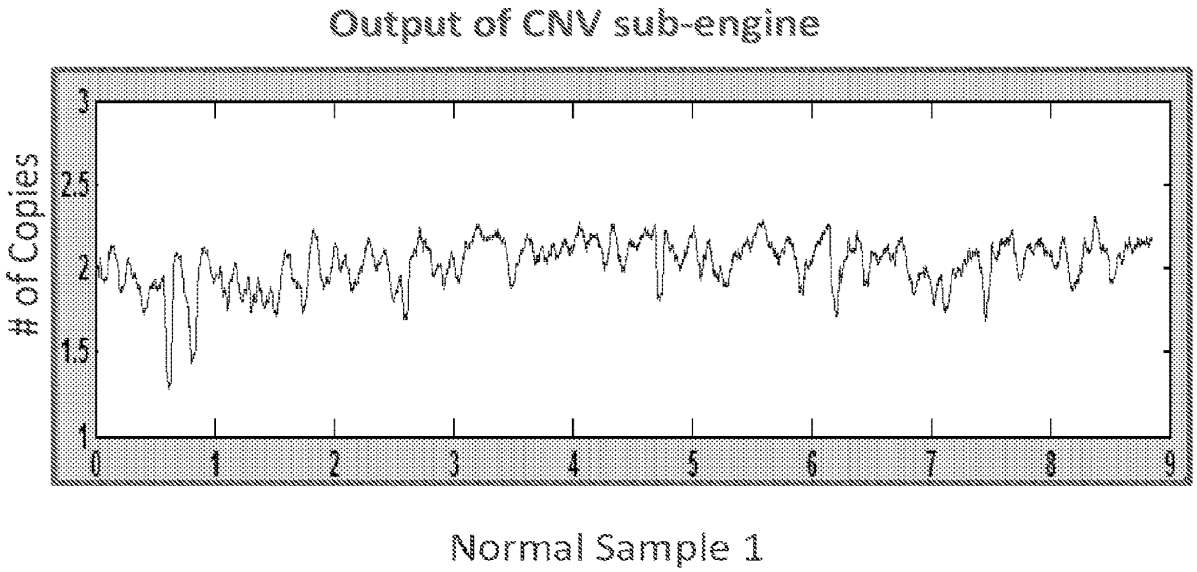

Output of CNV sub-engine
of Copies
3
2.5
2
1.5
1
0
1
2
3
4
5
6
7
8
9
Normal Sample 1

Fig. 4A

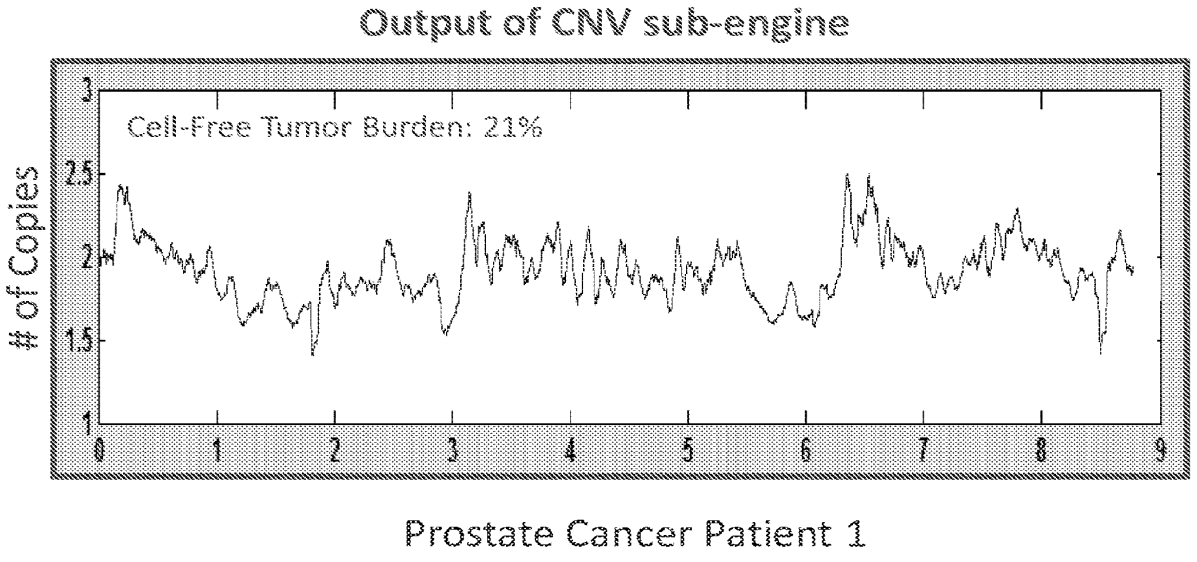

Output of CNV sub-engine
Cell-Free Tumor Burden: 21%
of Copies
3
2.5
2
1.5
1
0
1
2
3
4
5
6
7
8
9
Prostate Cancer Patient 1

Fig. 4B

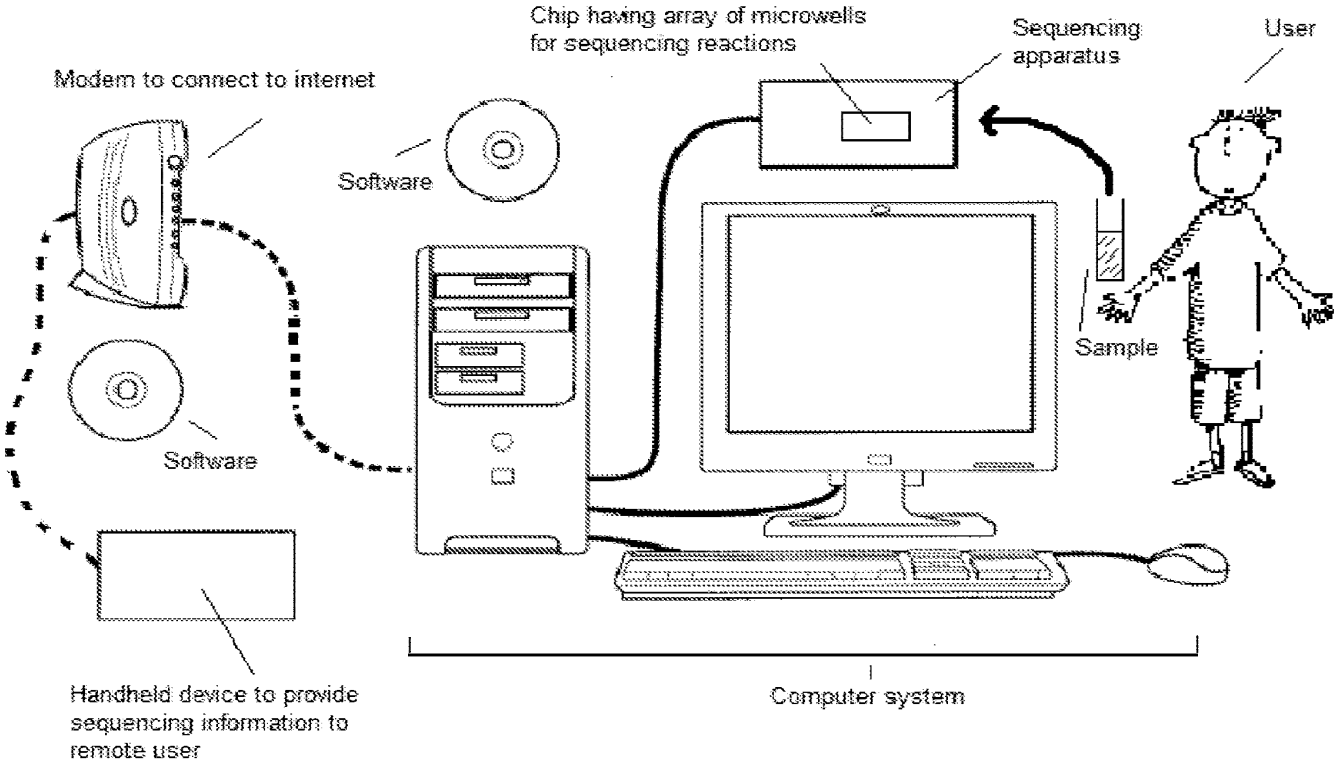

Chip having array of microwells for sequencing reactions
Sequencing apparatus
User
Modem to connect to internet
Software
Sample
Software
Handheld device to provide sequencing information to remote user
Computer system

Fig. 4C

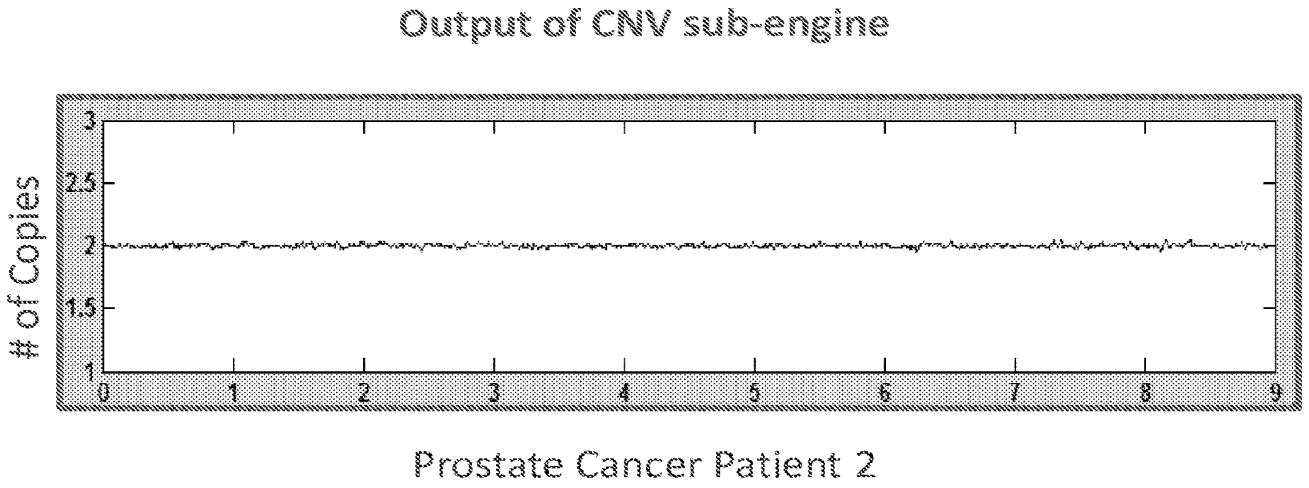

Output of CNV sub-engine
of Copies
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2
1.5
1
0
1
2
3
4
5
6
7
8
9
Prostate Cancer Patient 2

Fig. 5A

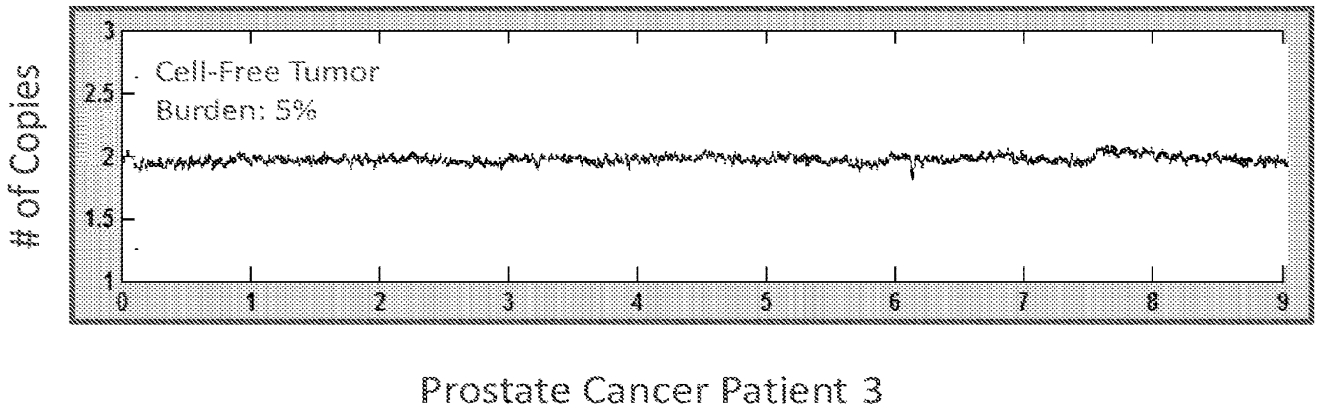

of Copies
Cell-Free Tumor
Burden: 5%
3
2.5
2
1.5
1
0
1
2
3
4
5
6
7
8
9
Prostate Cancer Patient 3

Fig. 5B

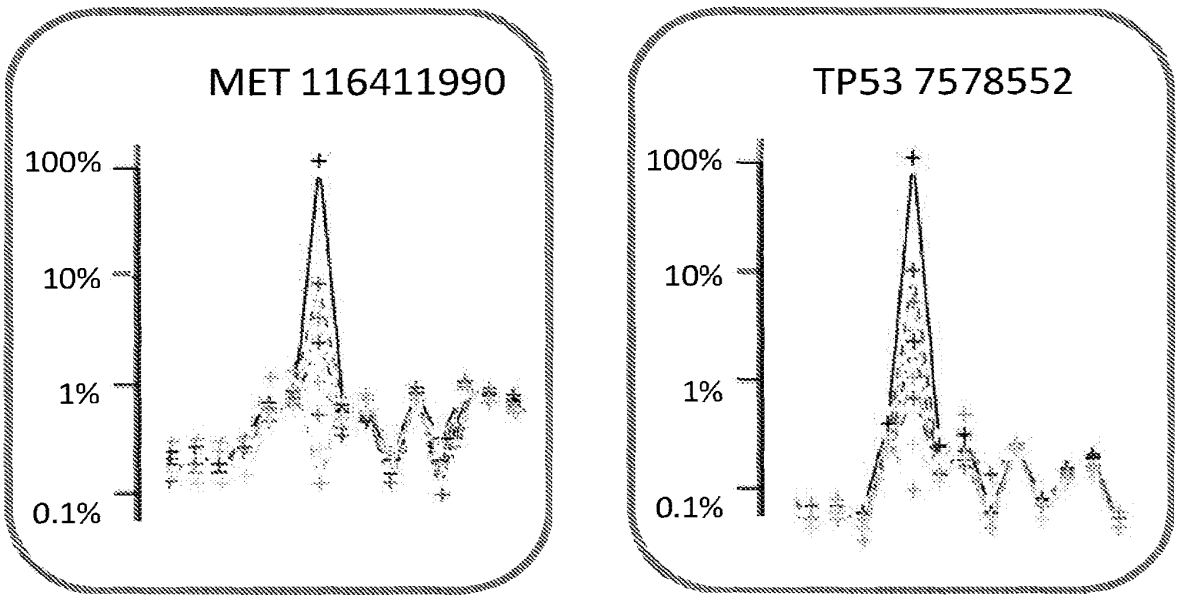

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TP53 7578552
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Fig. 6A

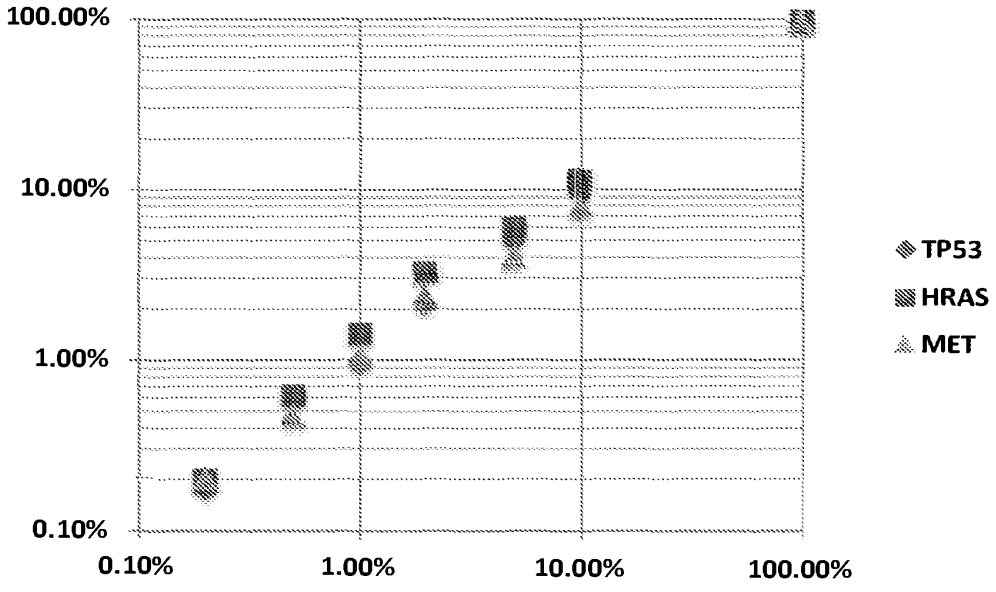

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HRAS
MET

Fig. 6B

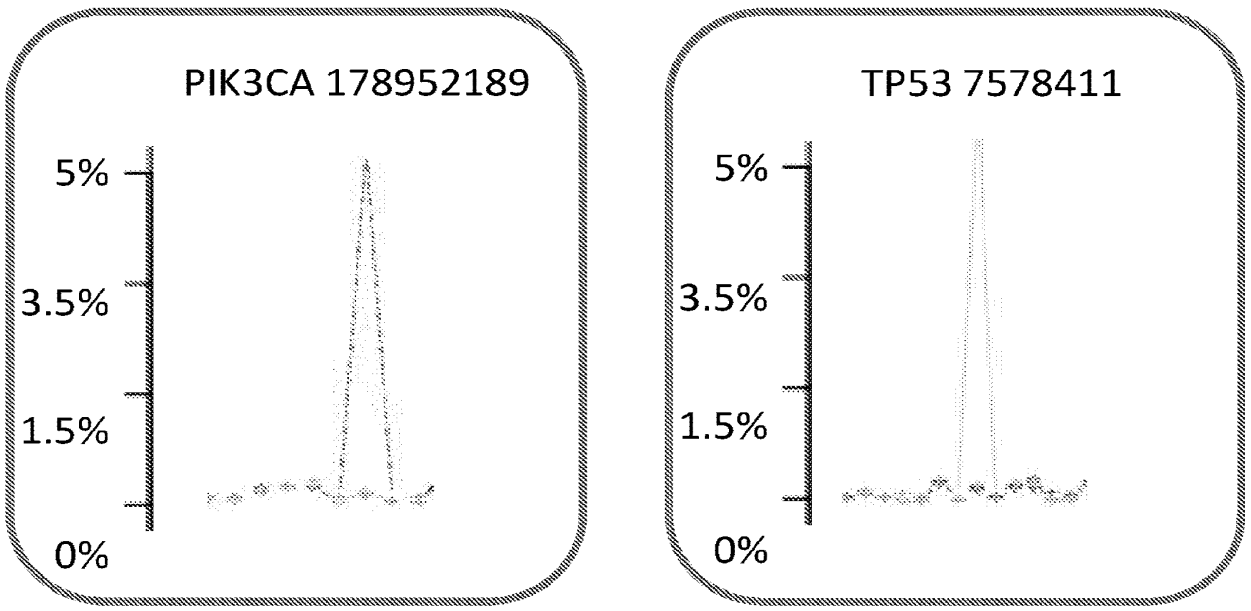

PIK3CA 178952189
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TP53 7578411
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Fig. 7A

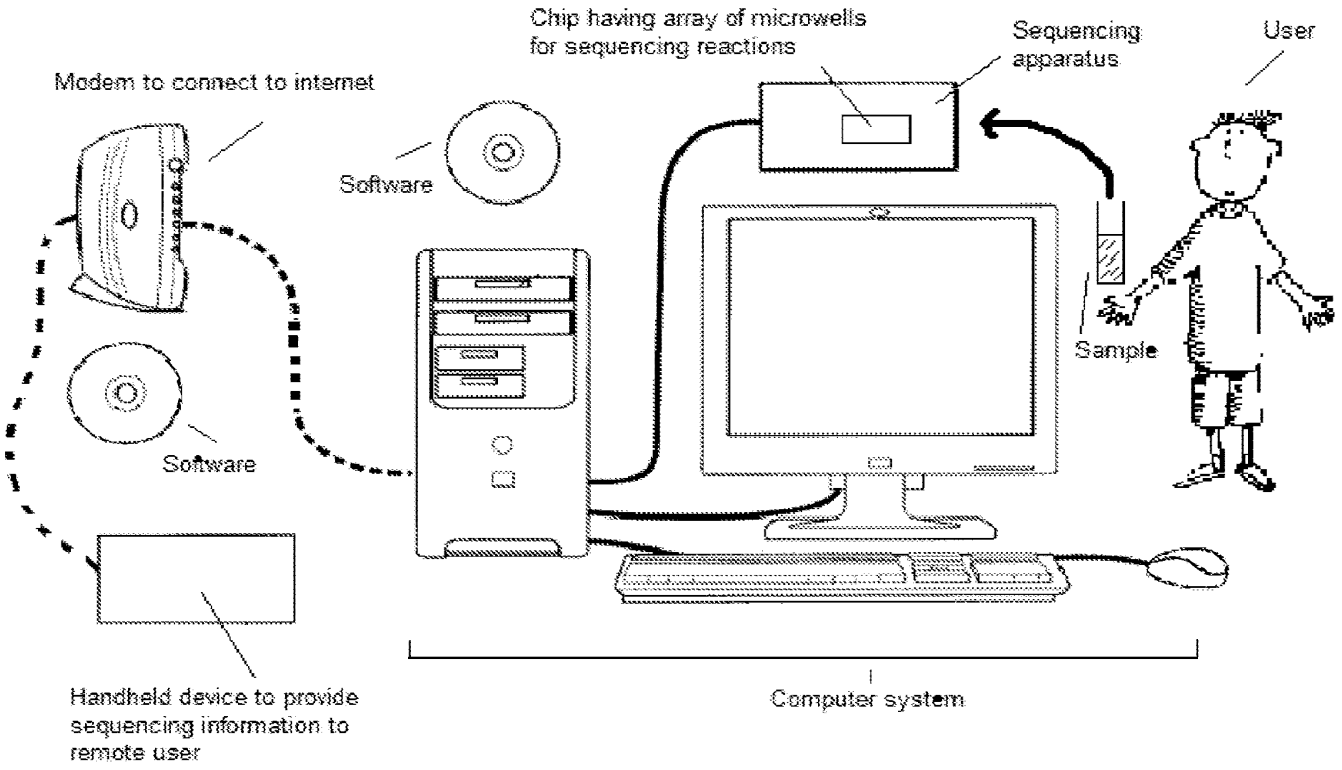

Chip having array of microwells for sequencing reactions
Sequencing apparatus
User
Modem to connect to internet
Software
Sample
Software
Handheld device to provide sequencing information to remote user
Computer system

Fig. 7B

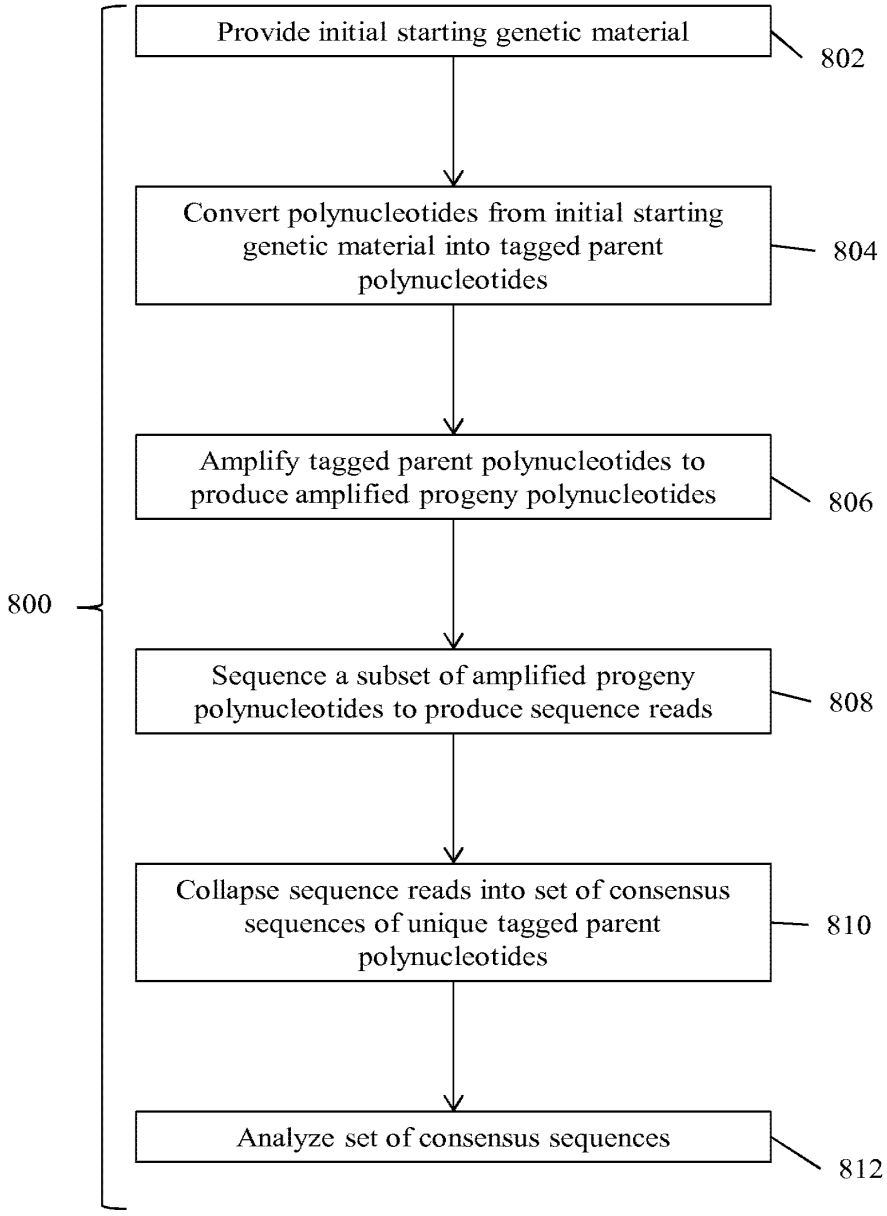

Provide initial starting genetic material
802
Convert polynucleotides from initial starting genetic material into tagged parent polynucleotides
804
Amplify tagged parent polynucleotides to produce amplified progeny polynucleotides
806
800
Sequence a subset of amplified progeny polynucleotides to produce sequence reads
808
Collapse sequence reads into set of consensus sequences of unique tagged parent polynucleotides
810
Analyze set of consensus sequences
812

Fig. 8

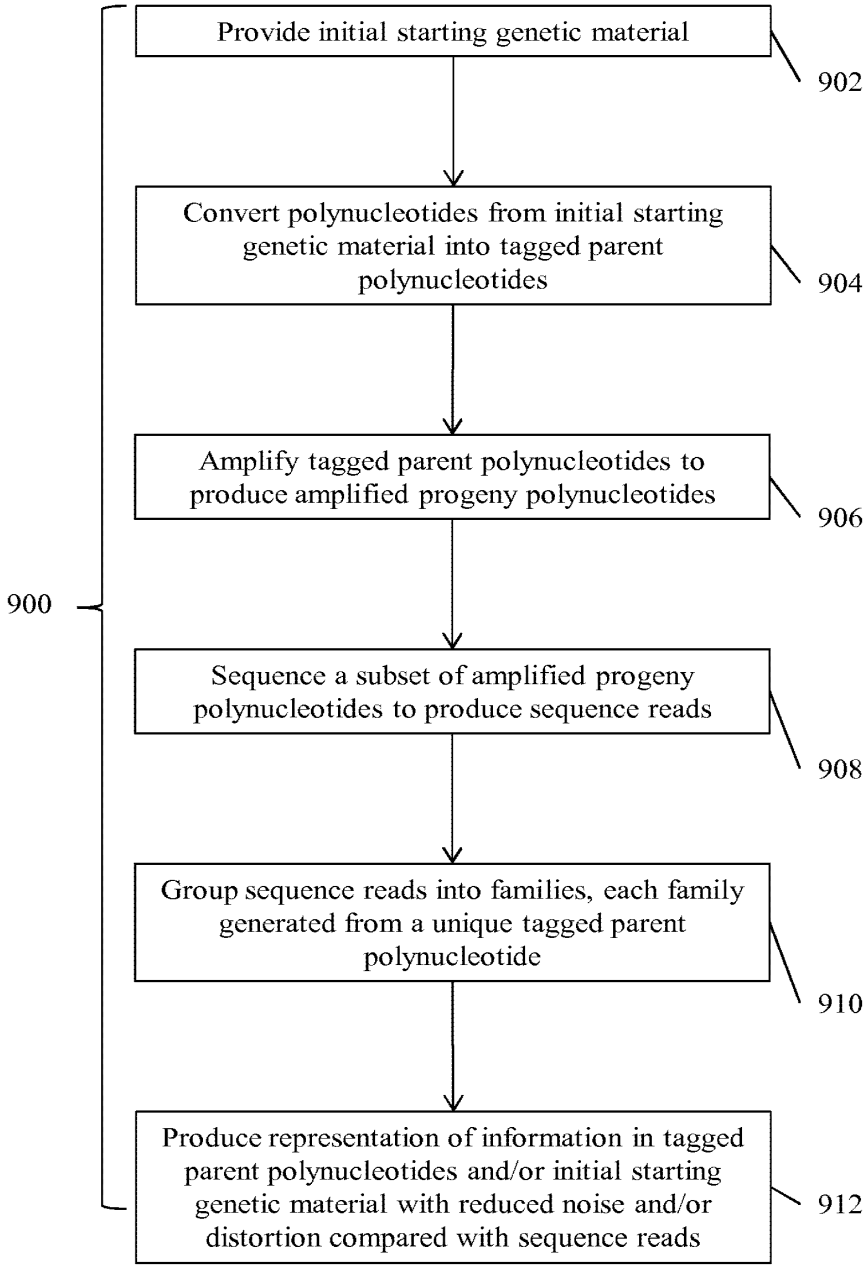

Provide initial starting genetic material
902
Convert polynucleotides from initial starting genetic material into tagged parent polynucleotides
904
Amplify tagged parent polynucleotides to produce amplified progeny polynucleotides
906
900
Sequence a subset of amplified progeny polynucleotides to produce sequence reads
908
Group sequence reads into families, each family generated from a unique tagged parent polynucleotide
910
Produce representation of information in tagged parent polynucleotides and/or initial starting genetic material with reduced noise and/or distortion compared with sequence reads
912

Fig. 9

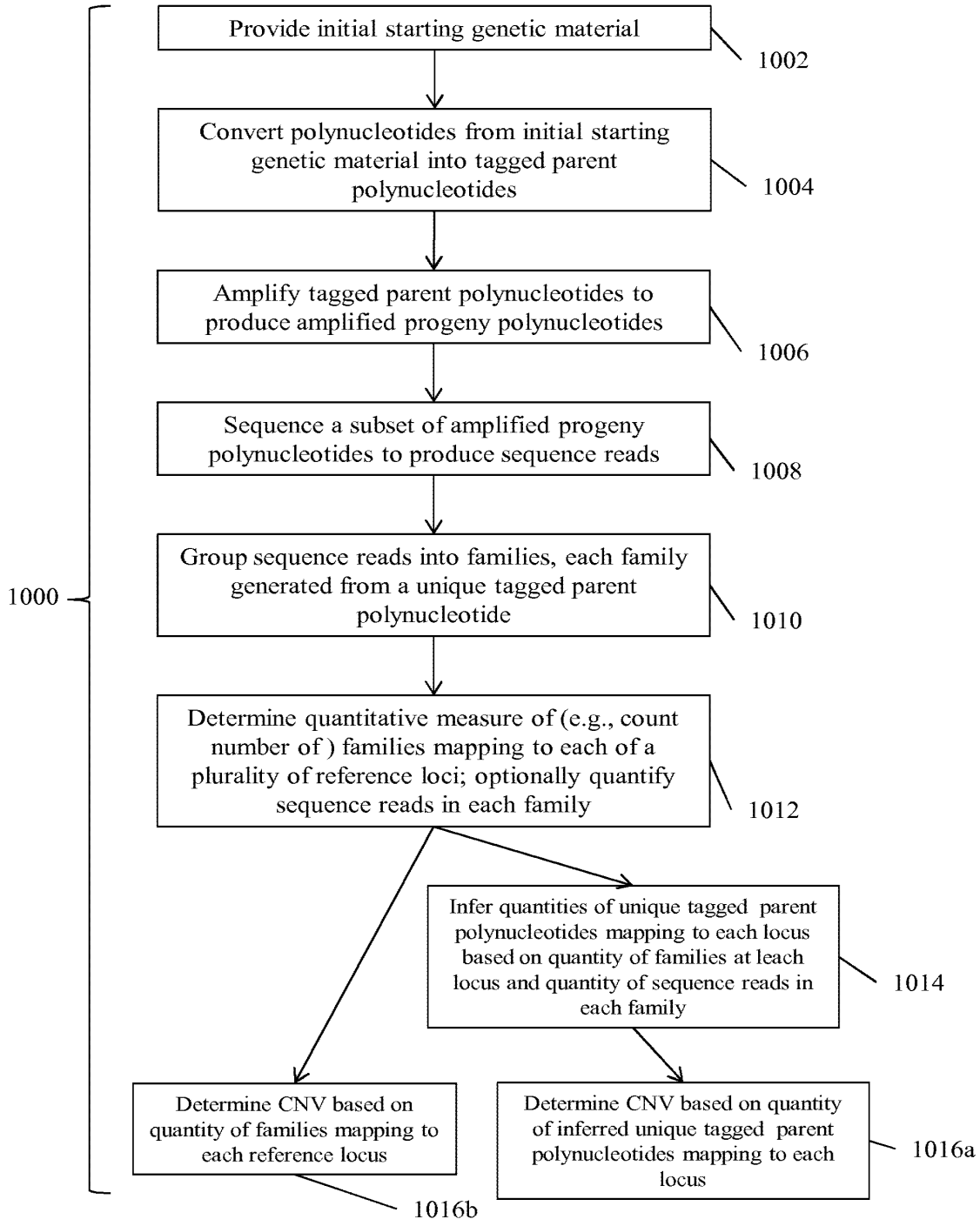

Provide initial starting genetic material
1002
Convert polynucleotides from initial starting genetic material into tagged parent polynucleotides
1004
Amplify tagged parent polynucleotides to produce amplified progeny polynucleotides
1006
Sequence a subset of amplified progeny polynucleotides to produce sequence reads
1008
Group sequence reads into families, each family generated from a unique tagged parent polynucleotide
1010
Determine quantitative measure of (e.g., count number of) families mapping to each of a plurality of reference loci; optionally quantify sequence reads in each family
1012
Infer quantities of unique tagged parent polynucleotides mapping to each locus based on quantity of families at leach locus and quantity of sequence reads in each family
1014
Determine CNV based on quantity of families mapping to each reference locus
1016b
Determine CNV based on quantity of inferred unique tagged parent polynucleotides mapping to each locus
1016a
1000

Fig. 10

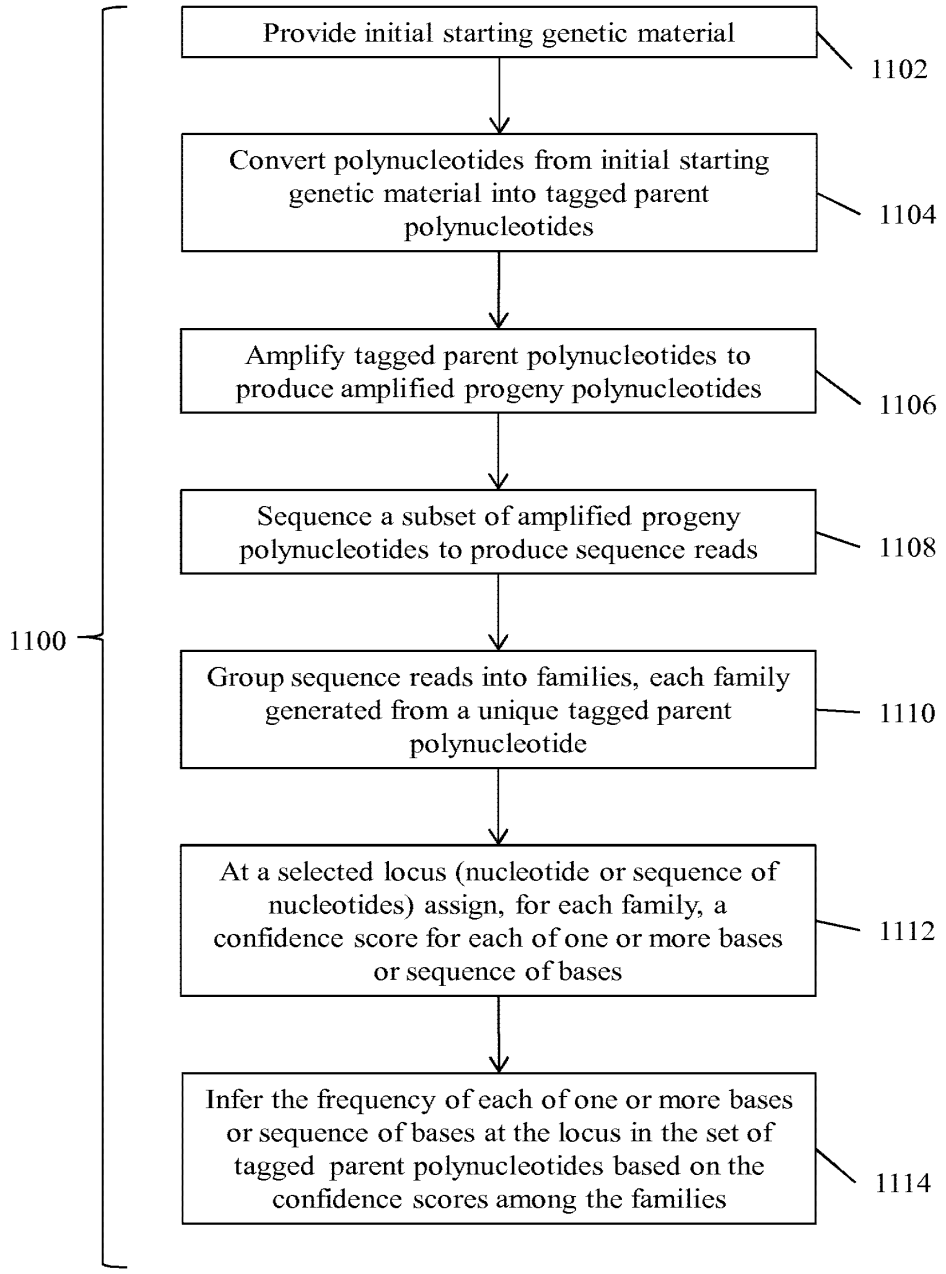

Provide initial starting genetic material
1102
Convert polynucleotides from initial starting genetic material into tagged parent polynucleotides
1104
Amplify tagged parent polynucleotides to produce amplified progeny polynucleotides
1106
Sequence a subset of amplified progeny polynucleotides to produce sequence reads
1108
1100
Group sequence reads into families, each family generated from a unique tagged parent polynucleotide
1110
At a selected locus (nucleotide or sequence of nucleotides) assign, for each family, a confidence score for each of one or more bases or sequence of bases
1112
Infer the frequency of each of one or more bases or sequence of bases at the locus in the set of tagged parent polynucleotides based on the confidence scores among the families
1114

Fig. 11

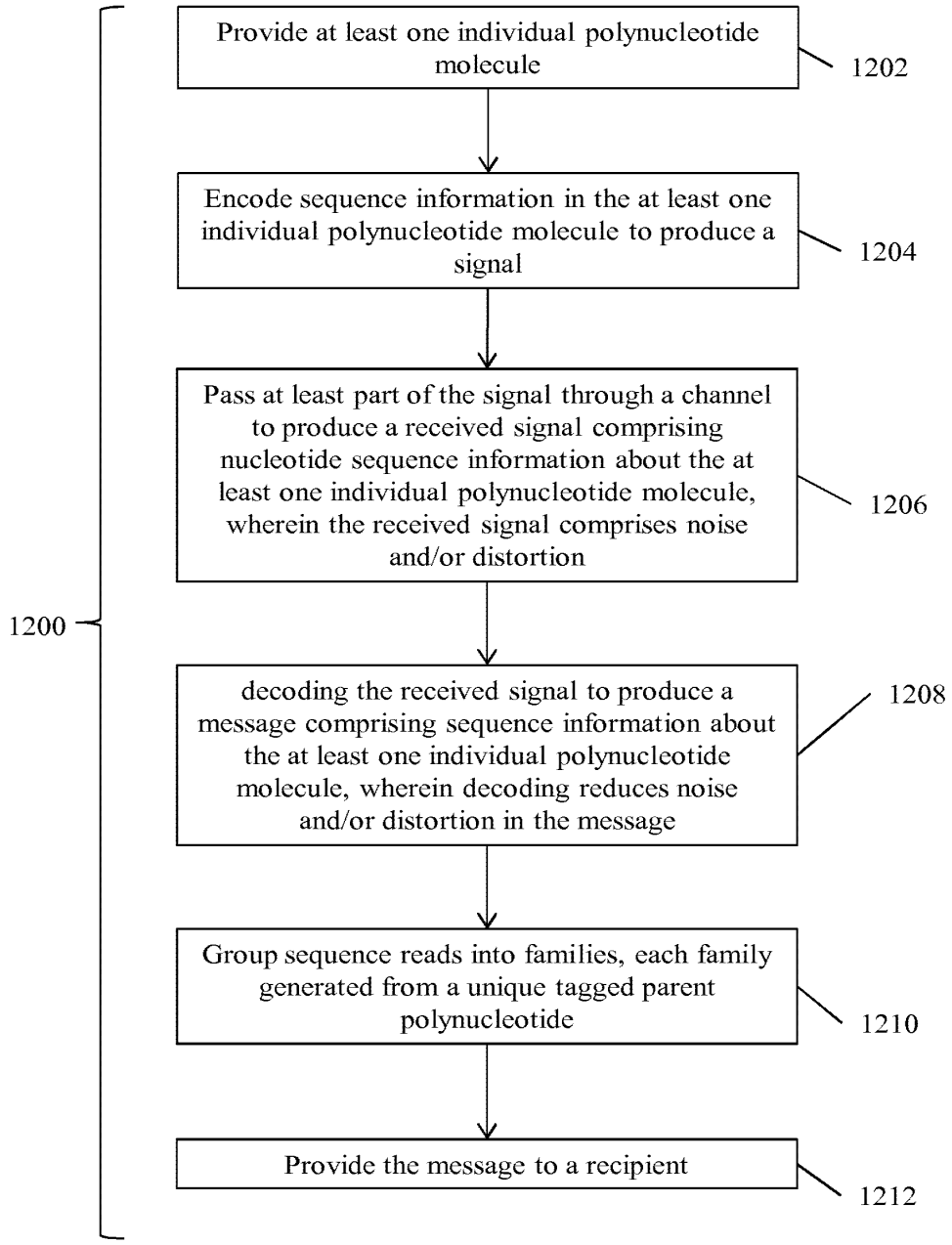

Provide at least one individual polynucleotide molecule
1202
Encode sequence information in the at least one individual polynucleotide molecule to produce a signal
1204
Pass at least part of the signal through a channel to produce a received signal comprising nucleotide sequence information about the at least one individual polynucleotide molecule, wherein the received signal comprises noise and/or distortion
1206
1200
decoding the received signal to produce a message comprising sequence information about the at least one individual polynucleotide molecule, wherein decoding reduces noise and/or distortion in the message
1208
Group sequence reads into families, each family generated from a unique tagged parent polynucleotide
1210
Provide the message to a recipient
1212

Fig. 12

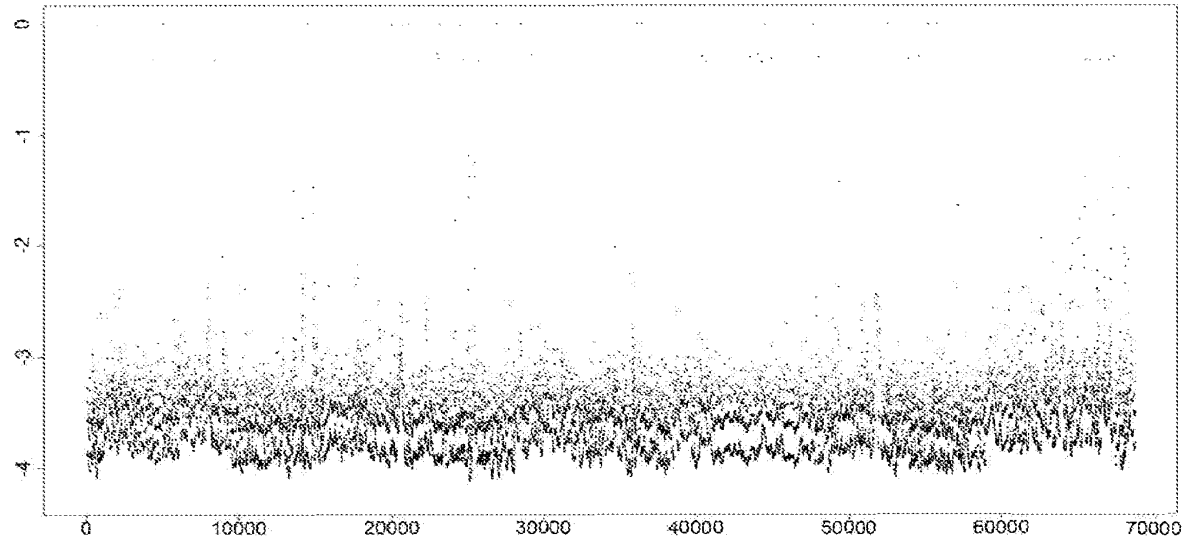


Fig. 13A

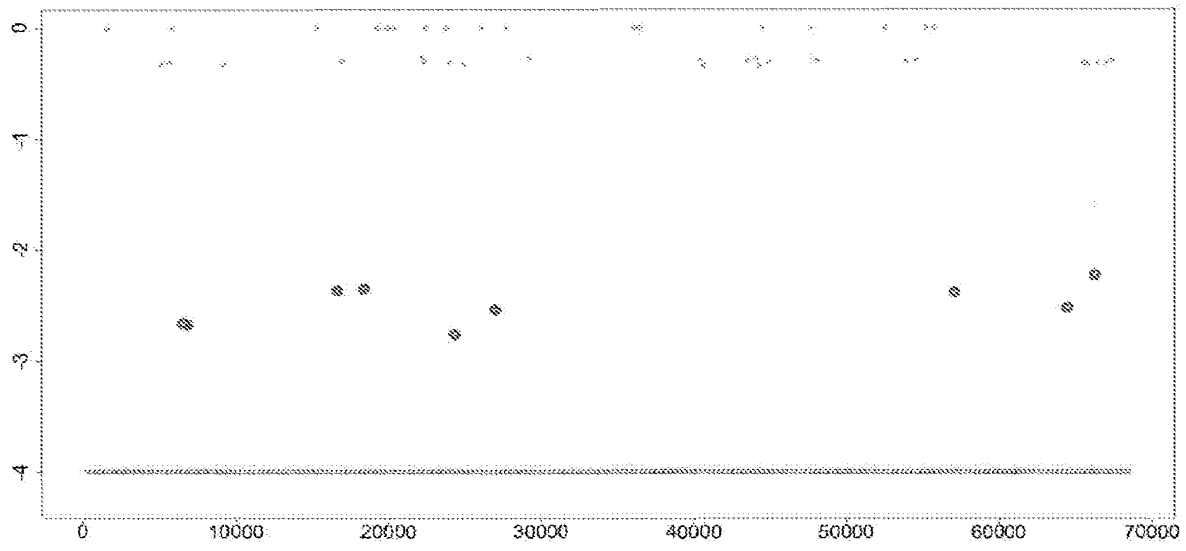


Fig. 13B

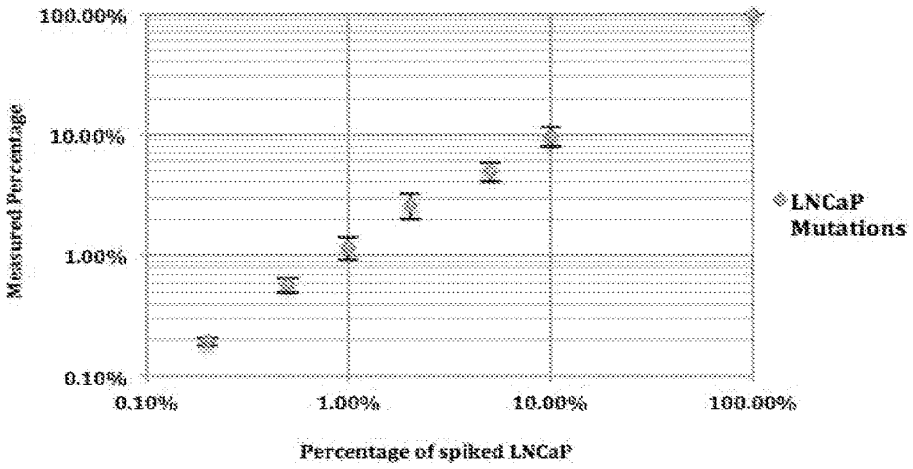

100.00%
10.00%
1.00%
0.10%
Measured Percentage
0.10%
1.00%
10.00%
100.00%
Percentage of spiked LNCaP
LNCaP Mutations

Fig. 14

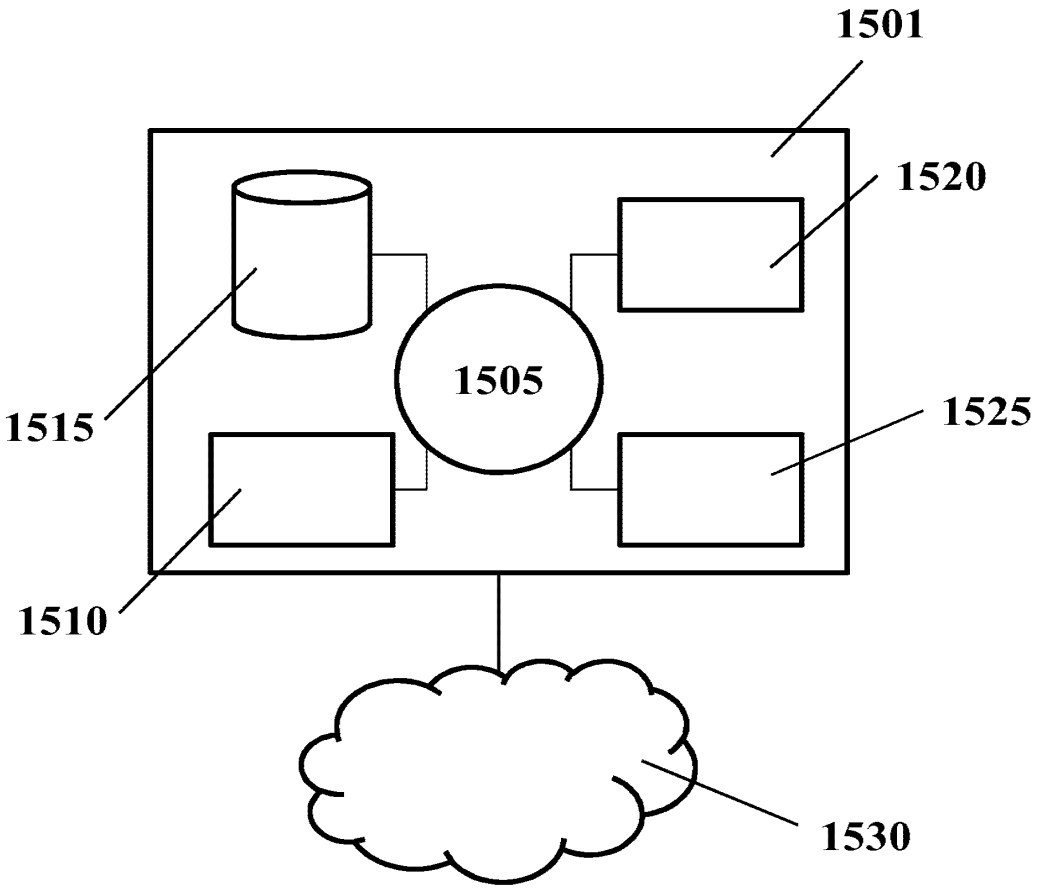


Fig. 15

PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 14/425,189

filed on March 2, 2015.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: AmirAli Talasaz Date (Optional): 10/23/15

Signature: _____

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1 minute 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.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-704.313GH0002US-C14

Filed as Large Entity

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	10	100	1000
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**6860**

Electronic Acknowledgement Receipt	
EFS ID:	37206028
Application Number:	16575128
International Application Number:	
Confirmation Number:	9440
Title of Invention:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-704.313GH0002US-C14
Receipt Date:	18-SEP-2019
Filing Date:	
Time Stamp:	17:53:44
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$6860
RAM confirmation Number	E20199HH54090866
Deposit Account	602231
Authorized User	Michelle Chan
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	2019-09-18_GH0002US-CON14_Track1.pdf	139562 25ea6360b73ca611eed6ba381bbf5fd009ee086e	no	2
Warnings:					
Information:					
2	Transmittal of New Application	2019-09-18_GH0002US-CON14_AppTrans.pdf	308809 e4cbe52c8529a7bb09268fe6fa791daeea0c6f60	no	2
Warnings:					
Information:					
3	Application Data Sheet	2019-09-18_GH0002US-CON14_ADS.pdf	1874515 aebee63f87545dafcc701954778b7330f312026e	no	9
Warnings:					
Information:					
4		2019-09-18_GH0002US-CON14_SpecAsFiled.pdf	468884 32f240066d05963a3b279d54d12c46d2baaeeb33	yes	87

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	82
Claims	83	86
Abstract	87	87

Warnings:					
Information:					
5	Drawings-only black and white line drawings	2019-09-18_GH0002US-CON14_Figures.pdf	618965 5d418ada0723848f0c171be73751f02bce31b020	no	16

Warnings:					
Information:					
6	Oath or Declaration filed	2019-09-18_GH0002US-CON14_DecParent.pdf	109807 138abe58c2cbfcfb8370ac704a92655b58806e23	no	1
Warnings:					
Information:					
7	Power of Attorney	2019-09-18_GH0002US-CON14_PoA_373B-parent.pdf	223387 8a62225f5f6979ed46c68ee8704f96bac9568a2a	no	3
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	41641 9366a8a1339da35baa48d778ec54c7a906d5f17d	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	3785570	

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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

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

First Named Inventor:	AmirAli TALASAZ	Nonprovisional Application Number (if known):	
Title of Invention:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION		

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

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

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

3. The applicable box is checked below:

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

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

---OR---

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

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

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

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

Signature /Timothy A. Hott/	Date 2019-09-18
Name (Print/Typed) Timothy A. Hott	Practitioner Registration Number 67740

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

☑ *Total of 1 forms are submitted.

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/80 (07-12)
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☒ Practitioners associated with Customer Number: 115823

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☒ The address associated with Customer Number: 115823

OR

☐

Firm or Individual Name			
Address			
City			
Country			
Telephone		Email	

Assignee
Guardant Health, Inc.
2686 Middlefield Rd, Suite D
Redwood City, CA 94063

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/SB/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	/[signature]/	Date *	9/5/13
Name	Helmy Eltoukhy	Telephone	
Title	CEO		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to 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.

5753826_1.DOC

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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Guardant Health, Inc.

Application No./Patent No.: 15/467,570 Filed/Issue Date: March 23, 2017

Titled: SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

Guardant Health, Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

☐ The extent (by percentage) of its ownership interest is ___%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 035180, Frame 0568, 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.

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

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.

/Gabriele A. Amodeo/	March 23, 2017
Signature	Date
Gabriele A. Amodeo	71,406
Printed or Typed Name	Title or Registration Number

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

PTO/SB/08a (02-18)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	16575128
	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4725536	A	1988-02-16	Fritsch et al.	
	2	4942124	A	1990-07-17	Church	
	3	5124246	A	1992-06-23	Urdea et al.	
	4	5149625	A	1992-09-22	Church et al.	
	5	5200314	A	1993-04-06	Urdea	
	6	5424186	A	1995-06-13	Fodor et al.	
	7	5424413	A	1995-06-13	Hogan et al.	
	8	5445934		1995-08-01	Fodor et al.	

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	Attorney Docket Number	42534-704.313

	9	5604097	A	1997-02-18	Brenner	
	10	5635352	A	1997-06-03	Urdea et al.	
	11	5635400	A	1997-06-03	Brenner	
	12	5648245	A	1997-07-15	Fire et al.	
	13	5654413	A	1997-08-05	Brenner	
	14	5656731	A	1997-08-12	Urdea	
	15	5658737	A	1997-08-19	Nelson et al.	
	16	5714330	A	1998-02-03	Brenner et al.	
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	19	5763175	A	1998-06-09	Brenner	

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	20	5800992		1998-09-01	Fodor et al.	
	21	5846719	A	1998-12-08	Brenner et al.	
	22	5854033	A	1998-12-29	Lizardi	
	23	5871928	A	1999-02-16	Fodor et al.	
	24	5925525	A	1999-07-20	Fodor et al.	
	25	5935793	A	1999-08-10	Wong	
	26	5952170	A	1999-09-14	Stroun et al.	Entire Document
	27	5968740	A	1999-10-19	Fodor et al.	
	28	5981176	A	1999-11-09	Wallace	
	29	5981179	A	1999-11-09	Lorinez et al.	
	30	6013445	A	2000-01-11	Albrecht et al.	

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	Attorney Docket Number	42534-704.313

	31	6020124	A	2000-02-01	Sorenson	
	32	6040138	A	2000-03-21	Lockhart et al.	
	33	6046005	A	2000-04-04	Ju et al.	
	34	6060596	A	2000-05-09	Lerner et al.	
	35	6117631	A	2000-09-12	Nilsen	
	36	6124092	A	2000-09-26	O'Neill et al.	
	37	6138077	A	2000-10-24	Brenner	
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	39	6172214	B1	2001-01-09	Brenner	
	40	6197506	B1	2001-03-06	Fodor et al.	
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	Attorney Docket Number	42534-704.313

	42	6242186	B1	2001-06-05	Salonen	
	43	6268152	B1	2001-07-31	Fodor et al.	
	44	6284460	B1	2001-09-04	Fodor et al.	
	45	6300077	B1	2001-10-09	Shuber et al.	
	46	6309822	B1	2001-10-30	Fodor et al.	
	47	6309823	B1	2001-10-30	Cronin et al.	
	48	6326148	B1	2001-12-04	Pauletti et al.	
	49	6355431	B1	2002-03-12	Chee et al.	
	50	6355432	B1	2002-03-12	Fodor et al.	
	51	6395491	B1	2002-05-28	Fodor et al.	
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	53	6440667	B1	2002-08-27	Fodor et al.	
	54	6440706	B1	2002-08-27	Vogelstein et al.	
	55	6451536	B1	2002-09-17	Fodor et al.	
	56	6458530	B1	2002-10-01	Morris et al.	
	57	6468744	B1	2002-10-22	Cronin et al.	
	58	6489114	B2	2002-12-03	Laayoun et al.	
	59	6492121	B2	2002-12-10	Kurane et al.	Entire Document
	60	6498012	B2	2002-12-24	Laken	Entire Document
	61	6503718	B2	2003-01-07	Shuber et al.	Entire Document
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	64	6544739	B1	2003-04-08	Fodor et al.	
	65	6551784	B2	2003-04-22	Fodor et al.	
	66	6576424	B2	2003-06-10	Fodor et al.	
	67	6582908	B2	2003-06-24	Fodor et al.	Entire Document
	68	6586177	B1	2003-07-01	Shuber	Entire Document
	69	6600996	B2	2003-07-29	Webster et al.	
	70	6629040	B1	2003-09-30	Goodlett et al.	
	71	6653077	B1	2003-11-25	Brenner	
	72	6753147	B2	2004-06-22	Vogelstein et al.	
	73	6849403	B1	2005-02-01	Shuber	Entire Document
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	75	6852488	B2	2005-02-08	Fodor et al.	
	76	6858412	B2	2005-02-22	Willis et al.	Entire Document
	77	6964846	B1	2005-11-15	Shuber	
	78	7163789	B2	2007-01-16	Chen et al.	
	79	7208275	B2	2007-04-24	Gocke et al.	
	80	7406385	B2	2008-07-29	Sorenson	Entire Document
	81	7410764	B2	2008-08-12	Gocke et al.	Entire Document
	82	7424368	B2	2008-09-09	Huang et al.	
	83	7424371	B2	2008-09-09	Kamentsky	Entire Document
	84	7537897	B2	2009-05-26	Brenner et al.	Entire Document
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	86	7704687	B2	2010-04-27	Wang et al.	Entire Document
	87	7727720	B2	2010-06-01	Dhallan	Entire Document
	88	7803929	B2	2010-09-28	Melkonyan et al.	Entire Document
	89	7811757	B2	2010-10-12	Shuber	Entire Document
	90	7822555	B2	2010-10-26	Huang et al.	
	91	7824889	B2	2010-11-02	Vogelstein et al.	Entire Document
	92	7838647	B2	2010-11-23	Hahn et al.	Entire Document
	93	7915015	B2	2011-03-29	Vogelstein et al.	Entire Document
	94	7935487	B2	2011-05-03	Gocke et al.	Entire Document
	95	7937225	B2	2011-05-03	Mishra et al.	Entire Document
	96	7957913	B2	2011-06-07	Chinitz et al.	

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	97	7972817	B2	2011-07-05	Kopreski	
	98	7981612	B2	2011-07-19	Shuber et al.	
	99	8094312	B2	2012-01-10	Ulmer	
	100	8168385	B2	2012-05-01	Brenner	Entire Document
	101	8195415	B2	2012-06-05	Fan et al.	
	102	8209130	B1	2012-06-26	Kennedy et al.	Entire Document
	103	8216789	B2	2012-07-10	Disis et al.	
	104	8236532	B2	2012-08-07	Ronaghi et al.	
	105	8361726	B2	2013-01-29	Gocke et al.	
	106	8383338	B2	2013-02-26	Kitzman et al.	Entire Document
	107	8383345	B2	2013-02-26	Shendure et al.	

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	Art Unit	
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	108	8455193	B2	2013-06-04	Travers et al.	
	109	8470996	B2	2013-06-25	Brenner	
	110	8481292	B2	2013-07-09	Casbon et al.	
	111	8603749	B2	2013-12-10	Gillevet	Entire Document
	112	8685678	B2	2014-04-01	Casbon et al.	
	113	8697408	B2	2014-04-15	Kucera et al.	Entire Document
	114	8704165	B2	2014-04-22	Huang	
	115	8715967	B2	2014-05-06	Casbon et al.	
	116	8722368	B2	2014-05-13	Casbon et al.	
	117	8728766	B2	2014-05-20	Casbon et al.	
	118	8741606	B2	2014-06-03	Casbon et al.	Entire Document

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	119	8775092	B2	2014-07-08	Colwell et al.	
	120	8835358	B2	2014-09-16	Fodor et al.	Entire Document
	121	8865410	B2	2014-10-21	Shendure et al.	Entire Document
	122	9018365	B2	2015-04-28	Brenner	Entire Document
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	36	Guardant Health vs. FMI Invalidity Exhibit A-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	37	Guardant Health vs. FMI Invalidity Exhibit A-2, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	38	Guardant Health vs. FMI Invalidity Exhibit A-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	

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	First Named Inventor	AmirAli TALASAZ
	Art Unit	
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	Attorney Docket Number	42534-704.313

	39	Guardant Health vs. FMI Invalidity Exhibit A-8, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	40	Guardant Health vs. FMI Invalidity Exhibit B-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	41	Guardant Health vs. FMI Invalidity Exhibit B-2, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	42	Guardant Health vs. FMI Invalidity Exhibit B-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	43	Guardant Health vs. FMI Invalidity Exhibit B-7, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	44	Guardant Health vs. FMI Invalidity Exhibit C-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	45	Guardant Health vs. FMI Invalidity Exhibit C-11, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
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	48	Guardant Health vs. FMI Invalidity Exhibit C-4, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
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	50	Guardant Health vs. FMI Invalidity Exhibit D-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	

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CERTIFICATION STATEMENT

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

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

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See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-10-18
Name/Print	Timothy A. Hott	Registration Number	67740

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	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
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	3	Guardant Health vs. FMI Invalidity Exhibit D-5, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	4	Guardant Health vs. FMI Second Amended Complaint dated March 6, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	5	Guardant Health vs. FMI Suppl Invalidity References dated February 15, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	6	Guardant Health vs. FMI Supplemental Invalidity Contentions dated March 29, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	7	Guardant Health vs. PGDx Amended Answer to Second Amended Complaint dated April 30, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	8	Guardant Health vs. PGDx Invalidity Claim Chart A, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	9	Guardant Health vs. PGDx Invalidity Claim Chart B, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	10	Guardant Health vs. PGDx Invalidity Claim Chart C, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	11	Guardant Health vs. PGDx Invalidity Claim Chart D, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	

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	12	Guardant Health vs. PGDx Invalidity Claim Chart E, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	13	Guardant Health vs. PGDx Invalidity Claim Chart F, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	14	Guardant Health vs. PGDx Invalidity Claim Chart G, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	15	Guardant Health vs. PGDx Invalidity Claim Chart H, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	16	Guardant Health vs. PGDx Invalidity Claim Chart I, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	17	Guardant Health vs. PGDx Invalidity Claim Chart J, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	18	Guardant Health vs. PGDx Invalidity Claim Chart K, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	19	Guardant Health vs. PGDx Invalidity Claim Chart L, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	20	Guardant Health vs. PGDx Invalidity Contentions dated June 25, 2018 (C.A. No. 17-cv-1623-LPS-CJB)	
	21	Guardant Health vs. PGDx Second Amended Complaint dated March 23, 2018 (C.A. No. 17-cv-1623-LPS-CJB)	
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	23	Guardant Health vs. PGDx Updated Invalidity Contentions dated March 29, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
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	Application Number	16575128
	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

	1	IPR2019-00130, Preliminary Response to Petition for Inter Partes Review U.S. 9,598,731, filed March 6, 2019	
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	3	IPR2019-00634, Petition for Inter Partes Review of U.S. Patent 9,840,743, dated February 1, 2019	
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	5	IPR2019-00636, Petition for Inter Partes Review of U.S. Patent 9,902,992, dated February 1, 2019	
	6	IPR2019-00637, Petition for Inter Partes Review of U.S. Patent 9,902,992, dated February 1, 2019	
	7	IPR2019-00652, Decision Granting Inter Partes Review U.S.9,834,822, issued August 19, 2019	
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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-10-18
Name/Print	Timothy A. Hott	Registration Number	67740

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16575128
	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

CERTIFICATION STATEMENT

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

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

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See attached certification statement.

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

☒ A certification statement is not submitted herewith.

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

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-10-18
Name/Print	Timothy A. Hott	Registration Number	67740

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First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-704.313

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	1	U.S. Provisional Application 61/613,413 ("Schmitt '413 provisional") (2012-03-20)	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16575128
	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

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	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

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If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16575128
	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

CERTIFICATION STATEMENT

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

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

OR

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

See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-10-18
Name/Print	Timothy A. Hott	Registration Number	67740

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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Electronic Acknowledgement Receipt

EFS ID:	37503804
Application Number:	16575128
International Application Number:	
Confirmation Number:	9440
Title of Invention:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-704.313
Receipt Date:	18-OCT-2019
Filing Date:	
Time Stamp:	18:26:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2019-10-18_GH0002US-CON14_IDSTrans.pdf	111858 4777b176277ff190a8eb6229f6822c2373eb1572	no	4

Warnings:

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2	Information Disclosure Statement (IDS) Form (SB08)	2019-10-18_GH0002US-CON14_1_OF_7.pdf	1067990 d66d5f1fa780f080147d76f7bb42e6c9dff89000	no	39
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3	Information Disclosure Statement (IDS) Form (SB08)	2019-10-18_GH0002US-CON14_2_OF_7.pdf	1057124 4c31fa574297fb3e745bbd4a1bc6381447dd494e	no	10
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6	Information Disclosure Statement (IDS) Form (SB08)	2019-10-18_GH0002US-CON14_5_OF_7.pdf	1057468 9925b7114d563fc8dcf35002760c07f62b077637	no	8
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7	Information Disclosure Statement (IDS) Form (SB08)	2019-10-18_GH0002US-CON14_6_OF_7.pdf	1057710 f43e9d0b888dd649653bb46605bc5005db0b0567	no	8

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8	Information Disclosure Statement (IDS) Form (SB08)	2019-10-18_GH0002US-CON14_7_OF_7.pdf	1056643 0e318eb593530b03e586baef09fe38112a5a523e	no	7

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Total Files Size (in bytes):	7521951

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

Inventor(s):	AmirAli TALASAZ	Confirmation No.:	9440
Serial No.:	16/575,128	Art Unit:	1636
Filing Date:	September 18, 2019	Examiner:	To be assigned
Title:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION		

FILED ELECTRONICALLY ON: October 18, 2019

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

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☒ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $240.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☐ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☐ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☐ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☒ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☒ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: 15/872,831; 16/283,635

Information Disclosure Statement(s) filed on: various

AND

☒ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 60-2231(Docket No. GH0002US-CON14).

Respectfully submitted,

Dated: October 18, 2019

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063

PATENT
Attorney Docket No. 42534-704.313/GH0002US-CON14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	AmirAli TALASAZ	Confirmation No.:	**9440**
Application No.	16/575,128	Examiner:	To be assigned
Filed:	September 18, 2019	Group Art Unit:	To be assigned
Title:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION	Customer No.	115823

Electronically Filed on: October 22, 2019

NOTICE OF CONCURRENT PROCEEDINGS

Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

The Applicant hereby notifies the Office of the following concurrent proceedings.

The following Patent Trial and Appeal Board proceedings of related patents are currently pending:

IPR # IPR2019-00634 (Patent No. 9,840,743; Application No. 15/467,570)

IPR # IPR2019-00652 (Patent No. 9,834,822; Application No. 15/492,659)

The Petitions for Inter Partes Review for the noted proceedings were filed February 1, 2019. If at any point the Examiner would like to be provided with copies of any contents of any related proceeding, Applicant (Patent Owner) will readily provide such copies upon request.

The Applicant believes that no fee is due with this submission. However, if a fee is due or to credit any overpayment, please charge any fees incorrected in connection with this submission or credit any overpayment to Deposit Account 60-2231 (GH0002US-CON14).

Respectfully submitted,

Date: October 22, 2019

By: /Timothy A. Hott/

Timothy A. Hott
Reg. No. 67,740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

PATENT
Attorney Docket No. 42534-704.313/GH0002US-CON14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	AmirAli TALASAZ	Confirmation No.:	**9440**
Application No.	16/575,128	Examiner:	To be assigned
Filed:	September 18, 2019	Group Art Unit:	To be assigned
Title:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION	Customer No.	115823

Electronically Filed on: October 22, 2019

NOTICE OF CONCURRENT PROCEEDINGS

Commissioner for Patents
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 CFR 1.56, MPEP 2001.06(c) and other duties of disclosure, Applicant hereby notifies the Office of recent pleadings by defendants Personal Genome Diagnostics, Inc. ("PGDx") and Foundation Medicine, Inc. ("FMI") alleging inequitable conduct for improper inventorship against Applicant in the ongoing litigation proceedings *Guardant Health, Inc. v. Personal Genome Diagnostics, Inc.* Civil Action No: 17-cv-1623-LPS-CJB and *Guardant Health, Inc. v. Foundation Medicine, Inc.* Civil Action No. 1:17-CV-01616-LPS-CJB, both filed in the United States District Court for the District of Delaware. The patents at issue in both litigations are US 9,598,731; US 9,834,822; US 9,840,743; and US 9,902,992.

Publicly available copies of documents describing the abovementioned pleadings by PGDx and FMI are submitted herewith. If at any point the Examiner would like

to be provided with copies of any additional contents of any related proceeding, Applicant will readily provide such copies upon request subject to relevant protective orders.

The Applicant believes that no fee is due with this submission. However, if a fee is due or to credit any overpayment, please charge any fees incorrected in connection with this submission or credit any overpayment to Deposit Account 60-2231 (GH0002US-CON14).

Respectfully submitted,

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Dear Commissioner:

Pursuant to 37 CFR 1.56, MPEP 2001.06(c) and other duties of disclosure, Applicant hereby notifies the Office of recent pleadings by defendants Personal Genome Diagnostics, Inc. ("PGDx") and Foundation Medicine, Inc. ("FMI") alleging, among other contentions, grounds for invalidity of US 9,598,731; US 9,834,822; US 9,840,743; and US 9,902,992 in the ongoing litigation proceedings *Guardant Health, Inc. v. Personal Genome Diagnostics, Inc.* Civil Action No: 17-cv-1623-LPS-CJB and *Guardant Health, Inc. v. Foundation Medicine, Inc.* Civil Action No. 1:17-CV-01616-LPS-CJB, both filed in the United States District Court for the District of Delaware.

Copies of documents describing the abovementioned pleadings by PGDx and FMI are submitted herewith. If at any point the Examiner would like to be provided with copies of

any additional contents of any related proceeding, Applicant will readily provide such copies upon request subject to relevant protective orders.

The Applicant believes that no fee is due with this submission. However, if a fee is due or to credit any overpayment, please charge any fees incorrected in connection with this submission or credit any overpayment to Deposit Account 60-2231 (GH0002US-CON14).

Respectfully submitted,

Date: October 22, 2019

By: /Timothy A. Hott/

Timothy A. Hott
Reg. No. 67,740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

CASREF,MEDIATION-CJB,PATENT

U.S. District Court
District of Delaware (Wilmington)
CIVIL DOCKET FOR CASE #: 1:17-cv-01616-LPS-CJB

Guardant Health, Inc. v. Foundation Medicine, Inc.
Assigned to: Judge Leonard P. Stark
Referred to: Judge Christopher J. Burke
Related Cases: 1:17-cv-00607-LPS-CJB
1:17-cv-00807-LPS-CJB
1:17-cv-01623-LPS-CJB
Cause: 35:271 Patent Infringement

Date Filed: 11/09/2017
Jury Demand: Both
Nature of Suit: 830 Patent
Jurisdiction: Federal Question

Plaintiff

Guardant Health, Inc.

represented by **Joseph J. Farnan , Jr.**
Farnan LLP
919 North Market Street
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ATTORNEY TO BE NOTICED

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Trevor J. Quist
Email: TQuist@sheppardmullin.com
TERMINATED: 08/17/2018
PRO HAC VICE

V.

Defendant

Foundation Medicine, Inc. represented by

Jeremy A. Tigan
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1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
302-351-9106
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ATTORNEY TO BE NOTICED

Movant

Illumina, Inc. represented by

Susan E. Morrison
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LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Counter Claimant

Foundation Medicine, Inc. represented by **Jeremy A. Tigan**
(See above for address)
ATTORNEY TO BE NOTICED

V.

Counter Defendant

Guardant Health, Inc. represented by **Joseph J. Farnan , Jr.**
(See above for address)
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Brian E. Farnan
(See above for address)
ATTORNEY TO BE NOTICED

Derek C. Walter
(See above for address)
ATTORNEY TO BE NOTICED

Edward R. Reines
(See above for address)
ATTORNEY TO BE NOTICED

Michael J. Farnan
(See above for address)
ATTORNEY TO BE NOTICED

Counter Claimant

Foundation Medicine, Inc. represented by **Jeremy A. Tigan**
(See above for address)
ATTORNEY TO BE NOTICED

V.

Counter Defendant

Guardant Health, Inc. represented by **Joseph J. Farnan , Jr.**
(See above for address)
LEAD ATTORNEY
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Brian E. Farnan
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Derek C. Walter
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EX1002.230

Edward R. Reines
(See above for address)
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Michael J. Farnan
(See above for address)
ATTORNEY TO BE NOTICED

Counter Claimant

Foundation Medicine, Inc. represented by **Jeremy A. Tigan**
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V.

Counter Defendant

Guardant Health, Inc. represented by **Joseph J. Farnan , Jr.**
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LEAD ATTORNEY
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Brian E. Farnan
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Trevor J. Quist
(See above for address)

EX1002.231

TERMINATED: 08/17/2018
PRO HAC VICE

Counter Claimant

Foundation Medicine, Inc. represented by **Jeremy A. Tigan**
(See above for address)
ATTORNEY TO BE NOTICED

V.

Counter Defendant

Guardant Health, Inc. represented by **Joseph J. Farnan , Jr.**
(See above for address)
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Brian E. Farnan
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Christopher M. Pistritto
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Derek C. Walter
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Trevor J. Quist
(See above for address)
TERMINATED: 08/17/2018
PRO HAC VICE

Date Filed	#	Docket Text
11/09/2017	1	

		COMPLAINT FOR PATENT INFRINGEMENT filed with Jury Demand against Foundation Medicine, Inc. - Magistrate Consent Notice to Pltf. (Filing fee $ 400, receipt number 0311-2263637.) - filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Civil Cover Sheet)(sar) (Entered: 11/09/2017)
11/09/2017	2	Notice, Consent and Referral forms re: U.S. Magistrate Judge jurisdiction. (sar) (Entered: 11/09/2017)
11/09/2017	3	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) US 9,598,731 B2;. (sar) (Entered: 11/09/2017)
11/09/2017		Summons Issued with Magistrate Consent Notice attached as to Foundation Medicine, Inc. on 11/9/2017. Requesting party or attorney should pick up issued summons at the Help Desk, Room 4209, or call 302-573-6170 and ask the Clerk to mail the summons to them. (sar) (Entered: 11/09/2017)
11/15/2017		Case Assigned to Judge Leonard P. Stark. Please include the initials of the Judge (LPS) after the case number on all documents filed. Associated Cases: 1:17-cv-01616-LPS, 1:17-cv-01623-LPS (rjb) (Entered: 11/15/2017)
11/16/2017	4	SUMMONS Returned Executed by Guardant Health, Inc.. Foundation Medicine, Inc. served on 11/10/2017, answer due 12/1/2017. (Farnan, Brian) (Entered: 11/16/2017)
11/21/2017	5	ORAL ORDER REFERRING CASE to Magistrate Judge Christopher J. Burke: IT IS HEREBY ORDERED that the above captioned case is referred to Magistrate Judge Christopher J. Burke to hear and resolve all pretrial matters, up to and including the resolution of case-dispositive motions, subject to 28 U.S.C. § 636(b) and any further Order of the Court; all subsequent filings in this action shall include the initials LPS-CJB after the case number. ORDERED by Judge Leonard P. Stark on 11/21/17. Associated Cases: 1:17-cv-01616-LPS, 1:17-cv-01623-LPS (ntl) (Entered: 11/21/2017)
11/21/2017	6	MOTION for Pro Hac Vice Appearance of Attorney Edward R. Reines and Derek C. Walter - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 11/21/2017)
11/27/2017		SO ORDERED D.I. 6 MOTION for Pro Hac Vice Appearance of Attorney Edward R. Reines and Derek C. Walter filed by Guardant Health, Inc.. Ordered by Judge Christopher J. Burke on 11/27/17. (mlc) (Entered: 11/27/2017)
11/27/2017	7	STIPULATION TO EXTEND TIME for Foundation Medicine to respond to the Complaint to January 16, 2018 - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 11/27/2017)
11/27/2017		SO ORDERED D.I. 7 STIPULATION TO EXTEND TIME for Foundation Medicine to respond to the Complaint to January 16, 2018 filed by Foundation Medicine, Inc.. Ordered by Judge Christopher J. Burke on 11/27/2017. (mlc) (Entered: 11/27/2017)
12/20/2017		Pro Hac Vice Attorney Derek C. Walter,Edward R. Reines for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d).,

		Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (crb) (Entered: 12/20/2017)
01/16/2018	8	ANSWER to 1 Complaint, with Jury Demand , COUNTERCLAIM against Guardant Health, Inc. by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/16/2018)
01/16/2018	9	Disclosure Statement pursuant to Rule 7.1: identifying Other Affiliate Roche Holdings Inc. for Foundation Medicine, Inc., Foundation Medicine, Inc. filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 01/16/2018)
01/17/2018		REMARK: The parties should be aware that the Court encourages the participation of newer attorneys in courtroom proceedings and at oral argument. Please see the Court's Standing Order Regarding Courtroom Opportunities for Newer Attorneys, a link to which is provided here for the parties' convenience: http://www.ded.uscourts.gov/sites/default/files/forms/StandingOrder2017.pdf (dlb) (Entered: 01/17/2018)
01/17/2018		ORAL ORDER: IT IS HEREBY ORDERED that the parties shall meet and confer and discuss, in person and/or by telephone, each of the matters listed on Chief Judge Stark's Case Management Checklist ("Checklist"). Within thirty (30) days from the date of this Order, the parties shall jointly file the following: (i) a copy of the "Checklist" indicating the names of Lead Counsel and Delaware Counsel for each party; (ii) a proposed Scheduling Order consistent with the Chief Judge Stark's Revised Patent Form Scheduling Order (with the exception that Paragraph (g) of the parties' proposed Scheduling Order shall be altered as follows: (a) the letter referenced in Paragraph (g)(ii) should be addressed to Judge Burke; (b) the time frames for the letters referenced in Paragraph (g)(iii) should be changed to 96 hours for the initial letter filed by the movant and 48 hours for the responsive letter filed by the opposing party; and (c) the parties should include an additional requirement that, after the Court has issued an order scheduling the discovery teleconference, the parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website); and (iii) a letter, not to exceed three pages, that contains the following: (a) a description of what this case is about; (b) the parties' positions regarding the disputes in the proposed Scheduling Order, and (c) a list of the three most significant topics (other than Scheduling Order disputes) discussed during the parties' review of the Checklist items, along with a brief description as to what was discussed as to those topics. Thereafter, the Court will schedule an in-person Case Management Conference/Rule 16 Scheduling Conference to be held with Judge Burke. The Checklist and Revised Patent Form Scheduling Order can be found on this Court's website (www.ded.uscourts.gov/judge/chief-judge-leonard-p-stark). Ordered by Judge Christopher J. Burke on 1/17/2017. (dlb) (Entered: 01/17/2018)
02/05/2018	10	First AMENDED COMPLAINT against Foundation Medicine, Inc.- filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9)(Farnan, Michael) (Entered: 02/05/2018)

02/05/2018	11	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) US 9,598,731 B2; US 9,834,822 B2; US 9,840,743 B2; . (Farnan, Michael) (Entered: 02/05/2018)
02/16/2018	12	Letter to The Honorable Christopher C. Burke from Brian E. Farnan regarding Scheduling Order - re Oral Order,,,,,,,,. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Farnan, Brian) (Entered: 02/16/2018)
02/20/2018	13	STIPULATION TO EXTEND TIME by which Foundation Medicine, Inc. shall respond to the First Amended Complaint to March 6, 2018 - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 02/20/2018)
02/21/2018		SO ORDERED D.I. 13 STIPULATION TO EXTEND TIME by which Foundation Medicine, Inc. shall respond to the First Amended Complaint to March 6, 2018 filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 2/21/2018. (dlb) (Entered: 02/21/2018)
02/22/2018		Oral Order Setting Telephonic Case Management/Scheduling Conference: A Case Management/Scheduling Teleconference is set for 3/19/2018 at 02:00 PM before Judge Christopher J. Burke. Because the proposed order is without any disputes, outside counsel may participate but are not required. Counsel for Plaintiff shall initiate the call. Ordered by Judge Christopher J. Burke on 2/22/2018. (dlb) (Entered: 02/22/2018)
03/01/2018	14	NOTICE OF SERVICE of Guardant Health, Inc.'s First Set of Interrogatories to Defendant (Nos. 1-5) and Guardant Health, Inc.'s First Set of Requests for Production of Documents and Things to Defendant (Nos. 1-61) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/01/2018)
03/06/2018	15	STIPULATION for Leave to File Second Amended Complaint by Guardant Health, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Farnan, Michael) (Entered: 03/06/2018)
03/06/2018		SO ORDERED D.I. 15 Stipulation for Leave to File Second Amended Complaint filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 3/6/2018. (dlb) (Entered: 03/06/2018)
03/06/2018	16	Second AMENDED COMPLAINT against Foundation Medicine, Inc.- filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12)(Farnan, Michael) (Entered: 03/06/2018)
03/06/2018	17	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) US 9,598,731 B2; US 9,834,822 B2; US 9,840,743 B2; US 9,902,992 B2; . (Farnan, Michael) (Entered: 03/06/2018)
03/09/2018	18	NOTICE OF SERVICE of Plaintiff's Identification of Accused Products, Asserted Patents, and Damages Model filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/09/2018)
03/12/2018	19	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Combining Case Management Conferences. (Farnan, Michael) (Entered: 03/12/2018)

03/13/2018		ORAL ORDER: The Court, having reviewed the parties' recent letters (D.I. 19 in Civil Action No. 17-1616-LPS-CJB and D.I. 17-18 in Civil Action No. 17-1623-LPS-CJB), hereby ORDERS as follows: The Court will hold one in-person Case Management/Scheduling Conference in which it will discuss both cases, on March 26, 2018 at 1:00 p.m. in Chambers. To the extent that any counsel has a conflict and cannot attend that in-person conference, they should notify the Court promptly, and in any event no later than March 15, 2018. To the extent any party wishes to make a proposal as to what the contours of a consolidated schedule applying to both cases should look like, they may do so by letter filed no later than March 21, 2018 (and may attach a copy of the proposed schedule to such a letter). Otherwise, the Court will utilize the parties' previously-submitted materials in addressing outstanding disputes at the conference. Ordered by Judge Christopher J. Burke on 3/13/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) Modified on 3/13/2018 (dlb). (Entered: 03/13/2018)
03/26/2018		Minute Entry for proceedings held before Judge Christopher J. Burke - Case Management/Scheduling Conference held on 3/26/2018. The Court heard the parties regarding any disputes and gave them key dates. Counsel shall confer regarding the rulings and submit one joint proposed schedule by April 2, 2018. (Court Reporter Brian Gaffigan) Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 03/26/2018)
03/26/2018	20	ANSWER to Amended Complaint, re: 16 Amended Complaint, with Jury Demand , COUNTERCLAIM against Guardant Health, Inc. by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 03/26/2018)
03/29/2018	21	Official Transcript of Case Managment Conference held on March 26, 2018 before Judge Christopher J. Burke. Court Reporter Brian Gaffigan, Telephone (302) 573-6360. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 4/19/2018. Redacted Transcript Deadline set for 4/30/2018. Release of Transcript Restriction set for 6/27/2018. (bpg) (Entered: 03/29/2018)
04/02/2018	22	PROPOSED ORDER Proposed Scheduling Order by Guardant Health, Inc.. (Attachments: # 1 Letter to The Honorable Christopher J. Burke)(Farnan, Brian) (Entered: 04/02/2018)
04/03/2018	23	MOTION for Pro Hac Vice Appearance of Attorney Eric J. Marandett, Maraget E. Ives, and Matthew S. Barrett of Choate Hall & Stewart LLP - filed by Foundation Medicine, Inc.. Motions referred to Christopher J. Burke.(Tigan, Jeremy) (Entered: 04/03/2018)
04/04/2018	24	SCHEDULING ORDER: Joinder of Parties due by 1/4/2019. Amended Pleadings due by 1/4/2019. Fact Discovery completed by 4/12/2019. Status Report due by 2/8/2019. Dispositive Motions due by 10/4/2019. A Motion Hearing is set for 1/24/2020 at 11:00 AM in Courtroom 2A before Judge Christopher J. Burke Claim Construction Opening Brief due by 9/12/2018. Claim Construction Answering Brief due by 10/19/2018. Claim Construction

		Reply Brief due by 11/2/2018. A Markman Hearing is set for 12/14/2018 at 11:00 AM in Courtroom 2A before Judge Christopher J. Burke. A Pretrial Conference is set for 5/8/2020 at 09:00 AM in Courtroom 6B before Judge Leonard P. Stark. A Jury Trial is set for 5/18/2020 at 09:30 AM in Courtroom 6B before Judge Leonard P. Stark. A Jury Trial is set for 6/8/2020 at 09:30 AM in Courtroom 6B before Judge Leonard P. Stark.. Signed by Judge Christopher J. Burke on 4/3/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 04/04/2018)
04/09/2018	25	MOTION for Pro Hac Vice Appearance of Attorney Diane Seol and John C. Calhoun of Choate Hall & Stewart LLP - filed by Foundation Medicine, Inc.. Motions referred to Christopher J. Burke.(Tigan, Jeremy) (Entered: 04/09/2018)
04/09/2018	26	NOTICE OF SERVICE of Guardant Health, Inc.'s Initial Disclosures filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/09/2018)
04/09/2018	27	NOTICE OF SERVICE of Foundation Medicine, Inc.'s Initial Disclosures filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/09/2018)
04/12/2018	28	NOTICE OF SERVICE of Foundation Medicine Inc.'s First Set of Requests for Production of Documents and Things to Plaintiff filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/12/2018)
04/13/2018	29	PROPOSED ORDER Proposed Protective Order by Guardant Health, Inc.. (Farnan, Brian) (Entered: 04/13/2018)
04/16/2018		SO ORDERED D.I. 29 Proposed Protective Order filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 4/16/2018. (dlb) (Entered: 04/16/2018)
04/16/2018	30	ANSWER to 20 Answer to Amended Complaint, Counterclaim by Guardant Health, Inc..(Farnan, Michael) (Entered: 04/16/2018)
04/26/2018	31	NOTICE OF SERVICE of (1) Responses to Guardant's First Set of Interrogatories (Nos. 1-5); and (2) Objections and Responses to Plaintiff's First Set of Requests for Production of Documents and Things (Nos. 1-61) filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/26/2018)
05/01/2018		SO ORDERED D.I. 25 MOTION for Pro Hac Vice Appearance of Attorney Diane Seol and John C. Calhoun of Choate Hall & Stewart LLP filed by Foundation Medicine, Inc., 23 MOTION for Pro Hac Vice Appearance of Attorney Eric J. Marandett, Maraget E. Ives, and Matthew S. Barrett of Choate Hall & Stewart LLP filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 5/1/2018. (dlb) (Entered: 05/01/2018)
05/03/2018	32	PROPOSED ORDER Proposed Stipulated Electronic Discovery Order by Guardant Health, Inc.. (Farnan, Brian) (Entered: 05/03/2018)
05/04/2018		SO ORDERED D.I. (35 in 1:17-cv-01623-LPS-CJB, 32 in 1:17-cv-01616-LPS-CJB) Proposed Stipulated Electronic Discovery Order filed by Guardant Health, Inc.. Ordered by Judge Christopher J. Burke on 5/4/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 05/04/2018)

05/08/2018	33	NOTICE OF SERVICE of First Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. to Guardant Health, Inc. (1-9) filed by Foundation Medicine, Inc.. (Attachments: # 1 Certificate of Service)(Taylor, James) (Entered: 05/08/2018)
05/14/2018	34	NOTICE OF SERVICE of Plaintiff Guardant Health, Inc.'s Responses and Objections to Defendant Foundation Medicine, Inc.'s First Set of Requests for Production of Documents and Things to Plaintiff (Nos. 1-55) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 05/14/2018)
05/17/2018		CASE REFERRED to Magistrate Judge Burke for Mediation. Please see Standing Order dated January 20, 2016, regarding disclosure of confidential ADR communications. A link to the standing order is provided here for your convenience at http://www.ded.uscourts.gov/general-orders/magistrate-judges-standing-order-adr-mediation (dlb) (Entered: 05/17/2018)
05/18/2018	35	NOTICE OF SERVICE of Plaintiff's ESI Disclosures filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 05/18/2018)
05/18/2018	36	NOTICE OF SERVICE of Disclosures Pursuant to Stipulated Electronic Discovery Order filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 05/18/2018)
05/25/2018	37	NOTICE OF SERVICE of Guardant Health's Infringement Claim Charts for U.S. Patent Nos. 9,598,731; 9,840,743; 9,834,822; and 9,902,992 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 05/25/2018)
06/04/2018	38	MOTION for Pro Hac Vice Appearance of Attorney Trevor J. Quist - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 06/04/2018)
06/06/2018		SO ORDERED D.I. (41 in 1:17-cv-01623-LPS-CJB, 38 in 1:17-cv-01616-LPS-CJB) MOTION for Pro Hac Vice Appearance of Attorney Trevor J. Quist filed by Guardant Health, Inc.. Ordered by Judge Christopher J. Burke on 6/6/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 06/06/2018)
06/07/2018	39	NOTICE OF SERVICE of Plaintiff's Responses and Objections to First Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 1-9) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 06/07/2018)
06/12/2018		Pro Hac Vice Attorney Trevor J. Quist for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(ceg) (Entered: 06/12/2018)
06/25/2018	40	NOTICE OF SERVICE of Defendant's Initial Invalidity Contentions filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 06/25/2018)
07/02/2018	41	

		ORDER Setting Mediation Conference: A Telephone Conference is set for 7/30/2018 at 10:45 AM before Judge Christopher J. Burke to discuss ADR. Signed by Judge Christopher J. Burke on 7/2/2018. (dlb) (Entered: 07/02/2018)
08/03/2018	42	STIPULATION TO EXTEND TIME for the parties to submit a proposal regarding page limits on claim construction briefing to August 31, 2018 - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 08/03/2018)
08/03/2018		SO ORDERED D.I. (46 in 1:17-cv-01623-LPS-CJB, 42 in 1:17-cv-01616-LPS-CJB) STIPULATION TO EXTEND TIME for the parties to submit a proposal regarding page limits on claim construction briefing to August 31, 2018 filed by Foundation Medicine, Inc.. Ordered by Judge Christopher J. Burke on 8/3/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 08/03/2018)
08/03/2018	43	NOTICE OF SERVICE of Plaintiff Guardant Health, Inc.'s List of Claim Terms and Proposed Constructions filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 08/03/2018)
08/07/2018	44	NOTICE OF SERVICE of Defendants' Preliminary Claim Construction Positions filed by Foundation Medicine, Inc..(Taylor, James) (Entered: 08/07/2018)
08/10/2018	45	NOTICE OF SERVICE of Plaintiff's First Supplemental Response to Joint Interrogatory Nos. 3 & 9 of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 08/10/2018)
08/16/2018	46	NOTICE requesting Clerk to remove Trevor J. Quist as co-counsel.. (Farnan, Michael) (Entered: 08/16/2018)
08/31/2018	47	CLAIM Construction Chart by Guardant Health, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I, # 10 Exhibit J, # 11 Exhibit K, # 12 Exhibit L, # 13 Exhibit M, # 14 Exhibit N, # 15 Exhibit O, # 16 Exhibit P, # 17 Exhibit Q, # 18 Exhibit R, # 19 Exhibit S, # 20 Exhibit T, # 21 Exhibit U, # 22 Exhibit V, # 23 Exhibit W, # 24 Exhibit X, # 25 Exhibit Y) (Farnan, Brian) (Entered: 08/31/2018)
08/31/2018	48	STIPULATION TO EXTEND TIME Claim Construction Briefing Limits to September 4, 2018 - filed by Guardant Health, Inc.. (Farnan, Michael) (Entered: 08/31/2018)
09/04/2018		SO ORDERED D.I. (54 in 1:17-cv-01623-LPS-CJB, 48 in 1:17-cv-01616-LPS-CJB) STIPULATION TO EXTEND TIME Claim Construction Briefing Limits to September 4, 2018 filed by Guardant Health, Inc..Ordered by Judge Christopher J. Burke on 9/4/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/04/2018)
09/04/2018	49	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Claim Construction Briefing Page Limits. (Farnan, Brian) (Entered: 09/04/2018)
09/05/2018		

		ORAL ORDER: The Court, having reviewed the parties' September 4, 2018 letter regarding their prospective proposals for claim construction briefing page limits, (D.I. (55 in 1:17-cv-01623-LPS-CJB, 49 in 1:17-cv-01616-LPS-CJB), HEREBY ORDERS as follows: (1) Plaintiff may have 20 pages for its opening brief and 15 pages for its reply brief.; and (2) Defendants may have either: (a) 25 pages for their answering brief and 10 pages for their sur-reply brief, or (b) 20 pages for their answering brief and 15 pages for their sur-reply brief. Ordered by Judge Christopher J. Burke on 9/5/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/05/2018)
09/21/2018	50	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Defendants' technology tutorial. (Tigan, Jeremy) (Entered: 09/21/2018)
09/21/2018	51	NOTICE OF SERVICE of Plaintiff's First Supplemental Response to Joint Interrogatory No. 6 of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 09/21/2018)
09/21/2018	52	NOTICE of filing the following Non-Paper material(s) in multi media format: two discs containing Plaintiff's Technology Tutorial. Original Non-paper material(s) to be filed with the Clerk's Office. Notice filed by Brian E. Farnan on behalf of Guardant Health, Inc. (Farnan, Brian) (Entered: 09/21/2018)
09/21/2018	53	[SEALED] CLAIM CONSTRUCTION OPENING BRIEF filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8)(Farnan, Brian) (Entered: 09/21/2018)
09/26/2018	54	MULTI MEDIA DOCUMENT filed by Guardant Health, Inc. in the form of a CD containing Plaintiff's Technology Tutorial. Filing related to (52 in 1:17-cv-01616-LPS-CJB) Notice of Filing Multi Media Materials,. (Media on file in Clerk's Office). Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/26/2018)
09/26/2018	55	MULTI MEDIA DOCUMENT filed by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc. in the form of a CD containing Defendants' Technology Tutorial. Filing related to (50 in 1:17-cv-01616-LPS-CJB, 56 in 1:17-cv-01623-LPS-CJB) Letter (Media on file in Clerk's Office). Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/26/2018)
09/28/2018	56	REDACTED VERSION of (53 in 1:17-cv-01616-LPS-CJB) Claim Construction Opening Brief, (59 in 1:17-cv-01623-LPS-CJB) Claim Construction Opening Brief, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-8)(Farnan, Brian) (Entered: 09/28/2018)
10/03/2018	57	NOTICE OF SERVICE of Guardant Health, Inc.'s Second Set of Requests for Production of Documents and Things to Defendant Foundation Medicine, Inc. (Nos. 62 - 81) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 10/03/2018)
10/10/2018		ORAL ORDER: The Court hereby ORDERS that by no later than November 30, 2018, the parties shall submit the joint letter required by Paragraph 14 of

		the Scheduling Order. (Civil Action No. 17-1616-LPS-CJB, D.I. 24 at 11; Civil Action No. 17-1623-LPS-CJB, D.I. 25 at 11) In addition to indicating (1) whether the parties request leave to present testimony at the claim construction hearing and (2) the amount of time the parties are requesting be allocated to them for the claim construction hearing, the parties' joint letter shall also indicate (3) the order in which the parties intend to present the claim terms at issue, including which side will present first for each term. Ordered by Judge Christopher J. Burke on 10/10/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 10/10/2018)
10/19/2018	58	CLAIM CONSTRUCTION ANSWERING BRIEF re 53 Claim Construction Opening Brief, filed by Foundation Medicine, Inc.. (Attachments: # 1 Exhibits 1-4)(Tigan, Jeremy) (Entered: 10/19/2018)
10/19/2018	59	DECLARATION re (58 in 1:17-cv-01616-LPS-CJB) Claim Construction Answering Brief, (68 in 1:17-cv-01623-LPS-CJB) Claim Construction Answering Brief *(Stacey Gabriel)* by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 10/19/2018)
10/19/2018	60	STATEMENT re (61 in 1:17-cv-01623-LPS-CJB, 54 in 1:17-cv-01616-LPS-CJB) Multi Media Document, *[Defendants' Comments on Plaintiff's Technology Tutorial]* by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 10/19/2018)
10/19/2018	61	STATEMENT *[Plaintiff's Comments On Defendants' Technology Tutorial]* by Guardant Health, Inc.. (Farnan, Brian) (Entered: 10/19/2018)
11/02/2018	62	NOTICE OF SERVICE of Defendant Foundation Medicine, Inc.'s Responses and Objections to Plaintiff Guardant Health, Inc.'s Second Set of Requests for Production of Documents and Things (Nos. 62-81) filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 11/02/2018)
11/02/2018	63	CLAIM CONSTRUCTION REPLY BRIEF re 58 Claim Construction Answering Brief filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 11/02/2018)
11/16/2018	64	CLAIM CONSTRUCTION SURREPLY BRIEF re 63 Claim Construction Reply Brief filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 11/16/2018)
11/27/2018	65	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding courtesy copies of the slides from Defendants' Technical Tutorial - re (50 in 1:17-cv-01616-LPS-CJB, 56 in 1:17-cv-01623-LPS-CJB) Letter. (Attachments: # 1 Defendants' Tutorial Presentation)(Tigan, Jeremy) (Entered: 11/27/2018)
11/30/2018	66	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Claim Construction Hearing Process. (Farnan, Michael) (Entered: 11/30/2018)
12/03/2018		ORAL ORDER: The Court, having reviewed the parties' joint letter regarding the upcoming claim construction hearing, (D.I. 66 in Civil Action No. 17-1616-LPS-CJB; D.I. 76 in Civil Action No. 17-1623-LPS-CJB), HEREBY ORDERS as follows: (1) The Court adopts the parties' proposal that 3 hours be

		allocated for the hearing, split evenly between Plaintiff and Defendants.; (2) The Court will hear argument on the terms in the order proposed by Defendants, for substantially the reasons offered by Defendants, (id. at 2).; and (3) In light of the dispute as to which side will present first, the Court will defer to the patent owner. (Id.) Plaintiff will present first for each term, followed by Defendants (with Plaintiff and then Defendants thereafter provided opportunity for brief rebuttal). Ordered by Judge Christopher J. Burke on 12/3/2018. (dlb) (Entered: 12/03/2018)
12/14/2018		Minute Entry for proceedings held before Judge Christopher J. Burke - Markman Hearing held on 12/14/2018. The Court took the matter under advisement. With respect to the newly raised argument relating to the dependent claim, Defendants may file a letter brief of no more than 2 single-spaced pages by no later than December 21, 2018. (Court Reporter John Donnelly (Veritext). Clerk: M. Crawford) Appearances: B. Farnan, D. Walter, S. Chi, E. Reines for Plaintiff; J. Tigan, E. Marandett, M. Barrett for Foundation Medicine, Inc.; D. Bilson, J. Re, S. Larson, B. Zimmerman, J. Helm for Defendant Personal Genome Diagnostics, Inc. and Personal Genome Diagnostics, Inc. Associated Cases: 1:17-cv-01623-LPS-CJB, 1:17-cv-01616-LPS-CJB(mlc) (Entered: 12/14/2018)
12/17/2018		ORAL ORDER: The Court HEREBY ORDERS as follows: During the December 14, 2018 Markman hearing, the parties discussed the deposition testimony of Defendants' expert Dr. Gabriel, which Dr. Gabriel provided in the inter partes review proceeding that followed claim construction briefing in this case. By no later than December 21, 2018, Plaintiff may submit a supplemental letter brief of no more than 3 single-spaced pages addressing this testimony and its impact on claim construction in this matter. By no later than January 2, 2019, Defendants may file a responsive supplemental letter brief of no more than 3 single-spaced pages on the same topic. Ordered by Judge Christopher J. Burke on 12/17/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 12/17/2018)
12/21/2018	67	Letter to The Honorable Christopher J. Burke from David A. Bilson regarding new argument raised by Plaintiff at Markman hearing. (Bilson, David) (Entered: 12/21/2018)
12/21/2018	68	Official Transcript of Claim Construction Hearing held on December 14, 2018 before Judge Christopher J. Burke. Court Reporter John P. Donnelley of Veritext Reporting, Telephone (302) 571-0510. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 1/11/2019. Redacted Transcript Deadline set for 1/22/2019. Release of Transcript Restriction set for 3/21/2019. (bpg) (Entered: 12/21/2018)
12/21/2018	69	STIPULATION TO EXTEND TIME to File Supplemental Responsive Letter Brief re: Gabriel Testimony to January 4, 2019 - filed by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 12/21/2018)
12/21/2018		

		SO ORDERED D.I. (86 in 1:17-cv-01623-LPS-CJB, 69 in 1:17-cv-01616-LPS-CJB) STIPULATION TO EXTEND TIME to File Supplemental Responsive Letter Brief re: Gabriel Testimony to January 4, 2019 filed by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc. Ordered by Judge Christopher J. Burke on 12/21/2018. Associated Cases: 1:17-cv-01623-LPS-CJB, 1:17-cv-01616-LPS-CJB(mlc) (Entered: 12/21/2018)
12/21/2018	70	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Claim Construction Expert Testimony. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3)(Farnan, Michael) (Entered: 12/21/2018)
01/04/2019	71	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Response to Guardant's December 21, 2018 Letter. (Tigan, Jeremy) (Entered: 01/04/2019)
01/07/2019		CORRECTING ENTRY: Transcript filed at D.I. 72 was removed from the docket (duplicate of D.I. 68). (ntl) (Entered: 01/07/2019)
01/11/2019	72	NOTICE of Subpoena (Chronix Biomedical, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/11/2019	73	NOTICE of Subpoena (Cynvenio Biosystems, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/11/2019	74	NOTICE of Subpoena (Natera, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/11/2019	75	NOTICE of Subpoena (Sequenom, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/11/2019	76	NOTICE of Subpoena (Verinata Health, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/18/2019	77	NOTICE to Take Deposition of Mark Sausen, Ph.D. on 2/26/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	78	NOTICE to Take Deposition of William Stevens on 2/27/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	79	NOTICE to Take Deposition of Victor Velculescu, M.D., Ph.D. on 2/28/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	80	NOTICE to Take Deposition of Douglas Ward on 2/25/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	81	NOTICE OF SERVICE of Foundation Medicine, Inc.'s First Amended Initial Disclosures filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	82	NOTICE to Take Deposition of Derek Bertocci on March 11, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	83	NOTICE to Take Deposition of Helmy Eltoukhy on March 27, 2019 - March 28, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)

01/18/2019	84	NOTICE to Take Deposition of Bill Getty on February 28, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	85	NOTICE to Take Deposition of Mark Jacobstein on February 18, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	86	NOTICE to Take Deposition of Rick Lanman on March 4, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	87	NOTICE to Take Deposition of Stefanie Mortimer on February 13, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	88	NOTICE to Take Deposition of Justin Odegaard on March 8, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	89	NOTICE to Take Deposition of Lai Mun Siew on February 22, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	90	NOTICE to Take Deposition of AmirAli Talasaz on March 18, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	91	NOTICE to Take Deposition of Michael Wiley on February 26, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/18/2019)
01/18/2019	92	NOTICE to Take Deposition of Foundation Medicine, Inc. on 3/22/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/24/2019	93	NOTICE OF SERVICE of Plaintiff's Supplemental Identification of Accused Products filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/24/2019)
01/25/2019	94	NOTICE OF SERVICE of Foundation Medicine, Inc.'s Second Set of Requests for Production of Documents and Things to Plaintiff Guardant Health, Inc. filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/25/2019)
01/30/2019	95	NOTICE OF SERVICE of Second Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. to Guardant Health, Inc. (10-12) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 01/30/2019)
01/30/2019	96	NOTICE OF SERVICE of Foundation Medicine, Inc.'s Second Set of Interrogatories to Plaintiff Guardant Health, Inc. filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 01/30/2019)
02/04/2019	97	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding response to Guardant's February 4, 2019 letter. (Phillips, John) (Entered: 02/04/2019)
02/05/2019	98	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Supplemental Claim Construction Brief Given Defendant's Recent IPR Petitions. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E)(Farnan, Brian) (Entered: 02/05/2019)
02/06/2019	99	NOTICE to Take Deposition of Guardant Health, Inc. on April 3, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Main Document 99 replaced on 2/6/2019) (ntl). (Entered: 02/06/2019)

02/06/2019		ORAL ORDER: The Court, having reviewed Plaintiff's February 5, 2019 letter, (Civil Action No. 17-1616-LPS-CJB, D.I. 98; Civil Action No. 17-1623-LPS-CJB, D.I. 129), HEREBY ORDERS that Plaintiff's request is GRANTED as follows: (1) By no later than February 13, 2019, Plaintiff shall file a supplemental claim construction brief of no more than 5 double-spaced pages to address Defendant Foundation Medicine, Inc.'s recent inter partes review petitions directed to three of the asserted patents; and (2) By no later than February 20, 2019, Defendants may file a joint responsive supplemental claim construction brief of no more than 5 double-spaced pages. Ordered by Judge Christopher J. Burke on 2/6/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 02/06/2019)
02/06/2019		CORRECTING ENTRY: Corrected document added to D.I. 99 per request of counsel. (ntl) (Entered: 02/06/2019)
02/08/2019	100	Joint STATUS REPORT by Guardant Health, Inc.. (Farnan, Brian) (Entered: 02/08/2019)
02/13/2019	101	STATEMENT *Plaintiff's Supplemental Claim Construction Brief* by Guardant Health, Inc.. (Attachments: # 1 Exhibit 9)(Farnan, Brian) (Entered: 02/13/2019)
02/15/2019	102	NOTICE OF SERVICE of (1) Defendant's Supplemental Identification of Invalidity References and (2) Defendant Foundation Medicine, Inc.'s Objections to Guardant Health, Inc.'s Fed. R. Civ. P. 30(b)(6) Notice of Deposition filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 02/15/2019)
02/20/2019	103	STATEMENT re (136 in 1:17-cv-01623-LPS-CJB, 101 in 1:17-cv-01616-LPS-CJB) Statement *Defendants' Supplemental Responsive Markman Brief* by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 02/20/2019)
02/25/2019	104	NOTICE OF SERVICE of Plaintiff's Responses and Objections to Second Set of Requests for Production of Documents and Things (Nos. 56-89) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 02/25/2019)
02/27/2019	105	MOTION for Pro Hac Vice Appearance of Attorney Christopher M. Pistritto and Justin L. Constant - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 02/27/2019)
02/27/2019		SO ORDERED D.I. (105 in 1:17-cv-01616-LPS-CJB, 141 in 1:17-cv-01623-LPS-CJB) MOTION for Pro Hac Vice Appearance of Attorney Christopher M. Pistritto and Justin L. Constant filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 2/27/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 02/27/2019)
03/01/2019	106	NOTICE to Take Deposition of Justin Odegaard on March 7, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 03/01/2019)
03/01/2019	107	NOTICE to Take Deposition of Mark Jacobstein on March 5, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 03/01/2019)
03/01/2019	108	

		NOTICE OF SERVICE of Final Infringement Contentions filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/01/2019)
03/01/2019	109	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s Responses and Objections to Foundation Medicine, Inc.'s Second Set of Interrogatories (Nos. 12 - 13) and (ii) Plaintiff's Responses and Objections to Second Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 10-12) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/01/2019)
03/04/2019	110	NOTICE to Take Deposition of Jeff Palmer on 3/5/2019 (Amended) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/04/2019)
03/04/2019	111	NOTICE OF SERVICE of Plaintiff Guardant Health, Inc.'s Responses and Objections to Foundation Medicine, Inc.'s Notice of Deposition Pursuant to Fed. R. Civ. P. 30(b)(6) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/04/2019)
03/06/2019		Pro Hac Vice Attorney Justin L. Constant and Christopher M. Pistritto for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (ceg) (Entered: 03/06/2019)
03/11/2019	112	NOTICE to Take Deposition of Travis Clark on 3/13/2019 (Amended) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/11/2019)
03/12/2019	113	Joint STIPULATION TO EXTEND TIME for the completion of fact depositions; and other non-expert discovery to May 1, 2019 and May 15, 2019 respectively - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 03/12/2019)
03/13/2019		SO ORDERED D.I. (113 in 1:17-cv-01616-LPS-CJB, 156 in 1:17-cv-01623-LPS-CJB) Joint STIPULATION TO EXTEND TIME for the completion of fact depositions; and other non-expert discovery to May 1, 2019 and May 15, 2019 respectively filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 3/13/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 03/13/2019)
03/19/2019	114	NOTICE to Take Deposition of Jason Hughes on 4/4/2019 filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/19/2019)
03/21/2019	115	NOTICE to Take Deposition of Doron Lipson on 4/24/2019 (Amended) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/21/2019)
03/28/2019	116	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s First Set of Common Interrogatories to Defendants (Nos. 1-8); (ii) Guardant Health, Inc.'s First Set of Requests for Admission by Defendant (Nos. 1-15); (iii) Guardant Health, Inc.'s Second Set of Interrogatories to Defendant (Nos. 6-8); and (iv) Guardant Health, Inc.'s Third Set of Requests for Production of Documents and Things to Defendant (Nos. 82-86) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/28/2019)
03/29/2019	117	NOTICE OF SERVICE of Defendant's Supplemental Invalidity Contentions filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 03/29/2019)

04/01/2019	118	NOTICE to Take Deposition of Guardant Health, Inc. on April 2, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/01/2019)
04/01/2019	119	NOTICE to Take Deposition of Daniel Simon on April 23, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/01/2019)
04/01/2019	120	NOTICE to Take Deposition of Darya Chudova on April 30, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/01/2019)
04/04/2019	121	NOTICE to Take Deposition of Helmy Eltoukhy on April 8, 2019 and April 9, 2019 (Updated) filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/04/2019)
04/08/2019	122	NOTICE OF SERVICE of Plaintiff Guardant Health, Inc.'s Responses and Objections to Foundation Medicine, Inc.'s Revised Notice of Deposition Pursuant to Fed. R. Civ. P. 30(b)(6) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	123	NOTICE of Subpoena to Ariosa Diagnostics, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	124	NOTICE of Subpoena to Roche Diagnostics Corporation by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	125	NOTICE of Subpoena to Roche Diagnostics Operations, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	126	NOTICE of Subpoena to Roche Holdings, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	127	NOTICE of Subpoena to Roche Molecular Systems, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	128	NOTICE of Subpoena to Roche Sequencing Solutions, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/10/2019	129	NOTICE to Take Deposition of Mark Kennedy on April 12, 2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/10/2019)
04/15/2019	130	NOTICE OF SERVICE of (1) Defendant Foundation Medicine, Inc.'s Second Set of Interrogatories to Guardant Health, Inc., (2) Foundation Medicine, Inc.'s Third Set of Requests for Production of Documents and Things to Plaintiff Guardant Health, Inc., and (3) Foundation Medicine, Inc.'s First Set of Requests for Admission filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/15/2019)
04/15/2019	131	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s Second Set of Common Interrogatories to Defendants (Nos. 9-11) and (ii) Guardant Health, Inc.'s Third Set of Interrogatories to Defendant (Nos. 9-10) filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 04/15/2019)
04/17/2019	132	NOTICE OF SERVICE of Third Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. to Guardant Health, Inc. (13-15) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 04/17/2019)

04/17/2019	133	NOTICE OF SERVICE of Foundation Medicine, Inc.'s First Supplemental Response to Guardant Health, Inc.'s Interrogatory No. 4 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/17/2019)
04/17/2019	134	NOTICE to Take Deposition of Tom Civik on 4/19/2019 filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 04/17/2019)
04/22/2019	135	NOTICE to Take Deposition of Foundation Medicine, Inc. on 5/1/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/22/2019)
04/22/2019	136	NOTICE of Subpoena to Brown Rudnick LLP by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/22/2019)
04/22/2019	137	NOTICE of Subpoena to Choate, Hall & Stewart LLP by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/22/2019)
04/22/2019	138	NOTICE of Subpoena to Knobbe Martens Olson & Bear, LLP by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/22/2019)
04/23/2019	139	NOTICE to Take Deposition of AmirAli Talasaz on April 30, 2019 and May 1, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/23/2019)
04/26/2019	140	NOTICE OF SERVICE of Plaintiff's Supplemental Responses and Objections to First Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 1, 7) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/26/2019)
04/29/2019	141	NOTICE to Take Deposition of Daniel Simon on May 15, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/29/2019)
04/29/2019	142	NOTICE to Take Deposition of Michael Wiley on May 15, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/29/2019)
04/29/2019	143	NOTICE to Take Deposition of Darya Chudova on May 16, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/29/2019)
04/29/2019	144	NOTICE of Subpoena Duces Tecum and Ad Testificandum by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 04/29/2019)
04/29/2019	145	NOTICE OF SERVICE of (1) Defendant Foundation Medicine, Inc.'s Objections to Guardant Health, Inc.'s Second Fed. R. Civ. P. 30(b)(6) Notice of Deposition and (2) Choate Hall & Stewart LLP's Responses and Objections to Guardant's Subpoena filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 04/29/2019)
04/30/2019	146	NOTICE OF SERVICE of Guardant Health, Inc.'s First Supplemental Initial Disclosures filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/30/2019)
05/06/2019	147	[SEALED] STIPULATION Regarding Filing of Amended Answer and Counterclaims and Third Amended Complaint by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Tigan, Jeremy) (Entered: 05/06/2019)

05/07/2019		SO ORDERED D.I. 147 Stipulation regarding filing of Amended Complaint, Answer and Counterclaims filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 5/7/2019. (dlb) (Entered: 05/07/2019)
05/07/2019	148	[SEALED] AMENDED ANSWER to 16 Amended Complaint,, COUNTERCLAIM against Guardant Health, Inc. by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 05/07/2019)
05/07/2019	149	[SEALED] Third AMENDED COMPLAINT against Foundation Medicine, Inc.- filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12) (Farnan, Brian) (Entered: 05/07/2019)
05/08/2019	150	STIPULATION TO EXTEND TIME to EXTEND the deadlines for: (i) Plaintiff to respond to Defendant's First Amended Answer to Plaintiff's Second Amended Complaint and Counterclaims and (ii) Defendant to respond to Plaintiff's Third Amended Complaint to 6/20/2019 - filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 05/08/2019)
05/09/2019		SO ORDERED D.I. 150 STIPULATION TO EXTEND TIME to EXTEND the deadlines for: (i) Plaintiff to respond to Defendant's First Amended Answer to Plaintiff's Second Amended Complaint and Counterclaims and (ii) Defendant to respond to Plaintiff's Third Amended Co filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 5/9/2019. (dlb) (Entered: 05/09/2019)
05/14/2019	151	REDACTED VERSION of 149 Amended Complaint, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-12)(Farnan, Brian) (Entered: 05/14/2019)
05/15/2019	152	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s Second Supplemental Initial Disclosures; (ii) Plaintiff's Supplemental Responses and Objections to Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 1, 4, 6, 7, 8, 10, 11); (iii) Guardant Health, Inc.'s Supplemental Responses and Objections to Foundation Medicine, Inc.'s Second Set of Interrogatories (No. 13); (iv) Guardant Health, Inc.'s Responses and Objections to Foundation Medicine, Inc.'s First Set of Requests for Admission (Nos. 1-35); (v) Guardant Health, Inc.'s Responses and Objections to Foundation Medicine, Inc.'s Third Set of Requests for Production of Documents and Things (Nos. 90-111); (vi) Guardant Health, Inc.'s Responses and Objections to Foundation Medicine, Inc.'s Second Set of Interrogatories (Nos. 3-13); and (vii) Supplemental Claim Charts filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 05/15/2019)
05/16/2019	153	NOTICE OF SERVICE of (1) Foundation Medicine, Inc.'s Responses and Objections to Guardant's Second Set of Common Interrogatories (Nos. 9-11) and (2) Foundation Medicine, Inc.'s Responses and Objections to Guardant's Third Set of Interrogatories (Nos. 9-10) filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 05/16/2019)
05/16/2019	154	NOTICE OF SERVICE of Plaintiff's Responses and Objections to Third Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal

		Genome Diagnostics, Inc. (Nos. 13-15) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 05/16/2019)
05/22/2019	155	REDACTED VERSION of 148 Amended Answer to Complaint, Counterclaim by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 05/22/2019)
05/22/2019	156	NOTICE of Subpoena to Testify at a Deposition in a Civil Action (to Gangwu Mei) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 05/22/2019)
05/24/2019	157	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Discovery Teleconference. (Farnan, Brian) (Entered: 05/24/2019)
05/30/2019	158	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' May 24, 2019 letters requesting discovery dispute teleconferences regarding 4 total discovery disputes. (D.I. (269 in 1:17-cv-01623-LPS-CJB), D.I. (157 in 1:17-cv-01616-LPS-CJB) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 24 in Civil Action No. 17-1616-LPS-CJB; D.I. 25 in Civil Action No. 17-1623-LPS-CJB), will be modified as follows with regard to these disputes: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference (involving all parties in both cases) is set for 6/17/2019 at 03:00 PM before Judge Christopher J. Burke. (3) By no later than June 5, 2019, any party seeking relief shall file with the Court a letter, not to exceed four (4) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than June 11, 2019, any party opposing the application for relief may file a letter, not to exceed four (4) pages, in no less than 12-point font, outlining that party (s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the disputes prior to the telephone conference and will, in that event, cancel the conference.Ordered by Judge Christopher J. Burke on 5/30/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 05/30/2019)
06/03/2019	159	STIPULATION TO EXTEND TIME Regarding Expert Discovery Deadlines to Various Dates - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 06/03/2019)
06/04/2019		SO ORDERED D.I. 159 STIPULATION TO EXTEND TIME Regarding Expert Discovery Deadlines to Various Dates filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 6/4/2019. (dlb) (Entered: 06/04/2019)
06/05/2019	160	[SEALED] Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Discovery Disputes. (Attachments: # 1 Exhibit 1-5)(Tigan, Jeremy) (Entered: 06/05/2019)
06/05/2019	161	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6)(Farnan, Michael) (Entered: 06/05/2019)

06/11/2019	162	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding IPR Proceeding. (Attachments: # 1 Exhibit A)(Farnan, Brian) (Entered: 06/11/2019)
06/11/2019	163	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Response to Guardant Health, Inc.'s June 5 2019 Letter. (Attachments: # 1 Exhibit 1-5)(Tigan, Jeremy) (Entered: 06/11/2019)
06/11/2019	164	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Response to Defendant's June 5, 2019 Letter - re 160 Letter. (Farnan, Michael) (Entered: 06/11/2019)
06/12/2019	165	REDACTED VERSION of 160 Letter by Foundation Medicine, Inc.. (Attachments: # 1 Exhibits 1-5)(Tigan, Jeremy) (Entered: 06/12/2019)
06/14/2019	166	ORAL ORDER: The Court hereby ORDERS that the discovery dispute teleconference scheduled for 6/17/2019 at 3:00 pm is hereby rescheduled for 6/17/2019 at 10:00 am. Ordered by Judge Christopher J. Burke on 6/14/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 06/14/2019)
06/17/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 6/17/2019. The Court heard argument. The Court considers Defendant Foundation Medicine Inc.'s dispute to be moot. The Court denied Plaintiff's motion without prejudice to renew if the estoppel issue becomes relevant. The transcript will serve as the Court's order. (Court Reporter Carrie Gold (Veritext). Clerk: M. Crawford) Appearances: B. Farnan, E. Reines, J. Constant for Plaintiff; J. Tigan, K. Jacobs, E. Marandett, M. Ives, M. Barrett, E. Miller for Defendant Foundation Medicine, Inc.; J. Phillips, S. Larson, J. Re for Defendant Personal Genome Diagnostics, Inc. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 06/17/2019)
06/19/2019	167	Joint MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 06/19/2019)
06/20/2019	168	[SEALED] ANSWER to Amended Complaint, re: 149 Amended Complaint, , COUNTERCLAIM against Guardant Health, Inc. by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 06/20/2019)
06/20/2019	169	[SEALED] MOTION to Dismiss for Failure to State a Claim - filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1)Motions referred to Christopher J. Burke.(Farnan, Michael) (Entered: 06/20/2019)
06/25/2019	170	Official Transcript of Telephone Conference held on June 17, 2019 before Judge Christopher J. Burke. Court Reporter Services by Veritext Legal Solutions, Telephone (302) 571-0150. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 7/16/2019. Redacted Transcript Deadline set for 7/26/2019. Release of Transcript Restriction set for 9/23/2019. (bpg) (Entered: 06/25/2019)

06/26/2019	171	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Request for Discovery Teleconference. (Tigan, Jeremy) (Entered: 06/26/2019)
06/27/2019	172	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' June 26, 2019 letter requesting a discovery dispute teleconference regarding 1 discovery dispute. (D.I. 303 in 1:17-cv-01623-LPS-CJB; D.I. 171 in 17-cv-01616-LPS-CJB) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 24 in Civil Action No. 17-1616-LPS-CJB; D.I. 25 in Civil Action No. 17-1623-LPS-CJB), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is set for 7/22/2019 at 4:00 PM before Judge Christopher J. Burke. (3) By no later than July 8, 2019, any party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than July 15, 2019, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 6/27/2019. Associated Cases: 1:17-cv-01623-LPS-CJB, 1:17-cv-01616-LPS-CJB(dlb) (Entered: 06/27/2019)
07/01/2019	173	STIPULATION TO EXTEND TIME to File Brief in Opposition to Plaintiff Guardant Health, Inc.'s Motion to Dismiss Pursuant to Federal Rule of Civil Procedure 12(b)(6) (D.I. 169) to July 12, 2019 - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 07/01/2019)
07/01/2019		SO ORDERED D.I. 173 STIPULATION TO EXTEND TIME to File Brief in Opposition to Plaintiff Guardant Health, Inc.'s Motion to Dismiss Pursuant to Federal Rule of Civil Procedure 12(b)(6) (D.I. 169) to July 12, 2019 filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 7/1/2019. (dlb) (Entered: 07/01/2019)
07/02/2019	174	STIPULATION regarding Plaintiff's Answer to Defendant's Counterclaim by Guardant Health, Inc.. (Farnan, Brian) (Entered: 07/02/2019)
07/02/2019	175	SO ORDERED D.I. 174 Stipulation regarding Plaintiff's Answer to Defendant's Counterclaim filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 7/2/2019. (mlc) (Entered: 07/02/2019)
07/02/2019	176	Joint MOTION for Teleconference to Resolve Discovery Dispute - filed by Foundation Medicine, Inc.. Motions referred to Christopher J. Burke.(Tigan, Jeremy) (Entered: 07/02/2019)
07/08/2019	177	NOTICE to Take Deposition of Gangwu Mei on July 11, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 07/08/2019)
07/08/2019	178	

		[SEALED] Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Discovery Disputes. (Attachments: # 1 Exhibit 1-9)(Tigan, Jeremy) (Entered: 07/08/2019)
07/12/2019	179	[SEALED] ANSWERING BRIEF in Opposition re 169 MOTION to Dismiss for Failure to State a Claim filed by Foundation Medicine, Inc..Reply Brief due date per Local Rules is 7/19/2019. (Attachments: # 1 Exhibit 1-3)(Tigan, Jeremy) (Entered: 07/12/2019)
07/15/2019	180	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendants' July 8, 2019 Letter - re (178 in 1:17-cv-01616-LPS-CJB, 323 in 1:17-cv-01623-LPS-CJB) Letter. (Farnan, Brian) (Entered: 07/15/2019)
07/15/2019	181	REDACTED VERSION of 178 Letter *to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Discovery Disputes* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 1-9)(Tigan, Jeremy) (Entered: 07/15/2019)
07/18/2019	182	REDACTED VERSION of 168 Answer to Amended Complaint, Counterclaim by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 07/18/2019)
07/18/2019	183	REDACTED VERSION of 179 Answering Brief in Opposition, by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 07/18/2019)
07/19/2019	184	MOTION permission to attend July 22, 2019 telephonic discovery conference regarding motion to compel certain Illumina Confidential documents - filed by Illumina, Inc.. Motions referred to Christopher J. Burke.(Morrison, Susan) (Entered: 07/19/2019)
07/19/2019		SO ORDERED D.I. (330 in 1:17-cv-01623-LPS-CJB, 184 in 1:17-cv-01616-LPS-CJB) MOTION permission to attend July 22, 2019 telephonic discovery conference regarding motion to compel certain Illumina Confidential documents filed by Illumina, Inc.. Ordered by Judge Christopher J. Burke on 7/19/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 07/19/2019)
07/19/2019	185	REPLY BRIEF re 169 MOTION to Dismiss for Failure to State a Claim filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2)(Farnan, Michael) (Entered: 07/19/2019)
07/22/2019	186	REDACTED VERSION of 169 MOTION to Dismiss for Failure to State a Claim by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1)(Farnan, Brian) (Entered: 07/22/2019)
07/23/2019	187	REDACTED VERSION of (324 in 1:17-cv-01623-LPS-CJB, 180 in 1:17-cv-01616-LPS-CJB) Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 07/23/2019)
07/25/2019	188	NOTICE OF SERVICE of (1) Expert Report of Stacey Gabriel, Ph.D. Regarding Invalidity and (2) Expert Report of Michael L. Metzker, Ph.D. filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 07/25/2019)
07/25/2019	189	NOTICE OF SERVICE of (i) Expert Report of Stephen L. Becker, Ph.D. with Regard to Foundation Medicine, Inc. and (ii) Expert Report of Gregory

		Cooper, Ph.D. filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 07/25/2019)
07/26/2019	190	ORAL ORDER: The Court hereby ORDERS that the discovery dispute teleconference regarding the parties' Joint Motion for a Teleconference to Resolve Discovery Dispute, (D.I. 176 in 17-1616-LPS-CJB; D.I. 313 in 17-1623-LPS-CJB), is rescheduled for 8/5/2019 at 4:00 PM before Judge Christopher J. Burke.Ordered by Judge Christopher J. Burke on 7/26/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 07/26/2019)
08/05/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 8/5/2019. The Court heard argument regarding Defendants' discovery dispute, (D.I. 176 in 17-1616-LPS-CJB; D.I. 313 in 17-1623-LPS-CJB), and took the matter under advisement. (Court Reporter Heather Triozzi. Clerk: M. Crawford) Appearances: B. Farnan, E. Reines, J. Constant for Plaintiff; K. Jacobs, E. Marandett, M. Ives for Defendant Foundation Medicine, Inc.; J. Phillips, B. Zimmerman, S. Larson, J. Re for Defendant Personal Genome Diagnostics, Inc.; S. Morrison, M. Amon for non-party Illumina, Inc. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 08/06/2019)
08/07/2019	191	ORAL ORDER: The Court, having reviewed the parties' discovery dispute motion relating to Defendants' request that Plaintiff be compelled to produce documents related to Dr. Eltoukhy's employment at Illumina, Inc. ("Illumina") and involvement with Guardant in the 2012 time period (the "Motion"), (D.I. 176 in Civil Action No. 17-1616-LPS-CJB; D.I. 313 in Civil Action No. 17-1623-LPS-CJB), and the parties' letter briefs relating thereto, (D.I. 178; D.I. 180 in Civil Action No. 17-1616-LPS-CJB; D.I. 323; D.I. 324 in Civil Action No. 17-1623-LPS-CJB), and having heard argument on August 5, 2019, hereby ORDERS as follows with respect to Defendants' Motion: (1) Plaintiff has returned to Illumina approximately 51,000 documents that could contain relevant information. By no later than August 14, 2019, Defendants shall: (a) meet and confer with Illumina to see if they can agree to a process for determining search terms and subsequent production of relevant, non-privileged documents from this category of documents; and (b) submit a joint status report (along with Plaintiff) indicating whether Defendant and Illumina have reached agreement on such a process, and if they have not, indicating the issues that remain in dispute and the parties and Illuminas respective positions. (2) There are approximately 4,000-5,000 additional documents in Plaintiff's control that have not been produced but that could contain relevant information. By no later than August 13, 2019, Defendants shall provide Plaintiff with a list of reasonable search terms. By no later than August 19, 2019, Plaintiff shall indicate whether it has any objections thereto. If there are no disputes, Plaintiff shall search the documents in this category utilizing the agreed-upon search terms and shall produce relevant, non-privileged documents promptly thereafter. If there are disputes regarding the search terms, the parties shall further meet and confer to attempt to resolve them. If the parties cannot resolve any further disputes relating to these documents, they shall utilize the Courts discovery dispute procedures. (3) Defendants' Motion is

		DENIED-AS-MOOT in light of the agreements reached among the parties and Illumina with respect to the documents at issue as described above. Ordered by Judge Christopher J. Burke on 8/7/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 08/07/2019)
08/12/2019	192	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Request for Discovery Teleconference. (Farnan, Michael) (Entered: 08/12/2019)
08/13/2019	193	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' August 12, 2019 letter requesting a discovery dispute teleconference regarding one discovery dispute. (D.I. 192) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 24), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is set for September 4, 2019 at 2:00 PM before Judge Christopher J. Burke. (3) By no later than August 21, 2019, any party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than August 28, 2019, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 8/13/2019. (dlb) (Entered: 08/13/2019)
08/13/2019	194	MOTION for Pro Hac Vice Appearance of Attorney Sophie F. Wang and Xing-Yin Ni - filed by Foundation Medicine, Inc.. Motions referred to Christopher J. Burke.(Tigan, Jeremy) (Entered: 08/13/2019)
08/13/2019	195	MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 08/13/2019)
08/14/2019		SO ORDERED D.I. 194 MOTION for Pro Hac Vice Appearance of Attorney Sophie F. Wang and Xing-Yin Ni filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 8/14/2019. (dlb) (Entered: 08/14/2019)
08/15/2019	196	Joint STATUS REPORT by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 08/15/2019)
08/21/2019	197	[SEALED] Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2)(Farnan, Michael) (Entered: 08/21/2019)
08/23/2019	198	NOTICE requesting Clerk to remove Matthew S. Barrett as co-counsel. Reason for request: No longer with firm. (Tigan, Jeremy) (Entered: 08/23/2019)
08/28/2019	199	REDACTED VERSION of 197 Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-2)(Farnan, Michael) (Entered: 08/28/2019)

08/28/2019	200	[SEALED] Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Response to Guardant Health, Inc.'s Letter Regarding Discovery Dispute. (Tigan, Jeremy) (Entered: 08/28/2019)
08/29/2019	201	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Discovery Teleconference. (Farnan, Brian) (Entered: 08/29/2019)
08/29/2019	202	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' August 29, 2019 letter requesting a discovery dispute teleconference regarding 1 discovery dispute. (D.I. (347 in 1:17-cv-01623-LPS-CJB, 201 in 1:17-cv-01616-LPS-CJB) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 24 in Civil Action No. 17-1616-LPS-CJB; D.I. 25 in Civil Action No. 17-1623-LPS-CJB), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is set for 9/16/2019 at 02:00 PM before Judge Christopher J. Burke. (3) By no later than 9/5/2019, any party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than 9/11/2019, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference.Ordered by Judge Christopher J. Burke on 8/29/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 08/29/2019)
08/29/2019	203	MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 08/29/2019)
09/04/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 9/4/2019. The Court heard argument regarding Plaintiff's discovery dispute, (D.I. 195), and took the matter under advisement. (Court Reporter Adam Miller. Clerk: M. Crawford) Appearances: M. Farnan, E. Reines, J. Constant for Plaintiff; J. Tigan, M. Ives, E. Miller, R. Vallabhaneni for Defendant. (mlc) (Entered: 09/04/2019)
09/04/2019	204	REDACTED VERSION of 200 Letter *to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Response to Guardant Health, Inc.'s Letter Regarding Discovery Dispute* by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 09/04/2019)
09/05/2019	205	ORAL ORDER: The Court, having reviewed the parties' discovery dispute motion relating to Plaintiff Guardant Health, Inc.'s ("Guardant") request that the protective order be modified to allow Guardant to disclose a subset of Defendant Foundation Medicine, Inc.'s (FMI) deposition transcripts and exhibits to Personal Genome Diagnostics, Inc. ("PGDx") for Guardant's defense of PGDx's antitrust counterclaim in related Civil Action No. 17-1623-LPS-CJB (the "Motion"), (D.I. 195), and the parties' letter briefs relating

		thereto, (D.I. 197; D.I. 200), and having heard argument on September 4, 2019, HEREBY GRANTS Guardant's Motion. In doing so, the Court notes that the movant bears the burden of demonstrating that the protective order should be modified. Genentech, Inc. v. Amgen, Inc., Consol. Civ. No. 17-1407-CFC, 2019 WL 1349464, at *2 (D. Del. Mar. 26, 2019). Modification of the terms of a protective order is appropriate if the moving party demonstrates "good cause" for the modification, and courts may consider the factors set out in Pansy v. Borough of Stroudsburg, 23 F.3d 772, 786 (3d Cir. 1994) in evaluating whether "good cause" exists. Id. The Court has considered the Pansy factors and finds that Guardant has met its burden for the following reasons: (1) The information that Guardant seeks to disclose appears to be a discrete, cabined amount of information, limited to three deposition transcripts and associated exhibits. (See D.I. 197 at 3); (2) Some amount of this information appears to be relevant in helping Guardant to combat PGDx"s antitrust counterclaim. The testimony of employees of a key market player (FMI) tending to suggest that Guardant does not have monopoly power would seem important to Guardant's defense of such a claim.; (3) Although Guardant's request is coming late in the case, it was made not long after Guardants attempt to bifurcate and stay discovery on PGDx's antitrust counterclaim in the related case was rejected by the Court. (See Civil Action No. 17-1623-LPS-CJB, D.I. 332) Therefore, the Court does not view Guardant's request as untimely.; (4) Based on the information that the Court has at this time, the Court cannot say that the scope of any future discovery requests from PGDx to FMI would wreak havoc on the case schedule.; and (5) The information at issue would only be provided to PGDx's outside counsel and would be governed by the same protective order agreed to by FMI. Therefore, the requested modification of the protective order is not likely to harm FMI's privacy interests. (See D.I. 197 at 3). Ordered by Judge Christopher J. Burke on 9/5/2019. (dlb) (Entered: 09/05/2019)
09/05/2019	206	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C)(Farnan, Brian) (Entered: 09/05/2019)
09/06/2019	207	REPORT AND RECOMMENDATION regarding claim construction. Please note that when filing Objections pursuant to Federal Rule of Civil Procedure 72 (b)(2), briefing consists solely of the Objections (no longer than ten (10) pages) and the Response to the Objections (no longer than ten (10) pages). No further briefing shall be permitted with respect to objections without leave of the Court. Objections to R&R due by 9/20/2019. Signed by Judge Christopher J. Burke on 9/6/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/06/2019)
09/09/2019	208	NOTICE OF SERVICE of Guardant's Expert Rebuttal Report of Gregory Cooper, Ph.D. filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 09/09/2019)
09/09/2019	209	NOTICE OF SERVICE of (1) Expert Report of Gary Benson, Ph.D., (2) Rebuttal Expert Report and Disclosure of Julie L. Davis, and (3) Rebuttal Expert Report of Michael L. Metzker, Ph.D. filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 09/09/2019)

09/10/2019	210	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Supplemental Claim Construction Authority. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Farnan, Brian) (Entered: 09/10/2019)
09/10/2019	211	Letter to The Honorable Christopher J. Burke from Karen Jacobs regarding response to Plaintiff's purported "supplemental authority" on claim construction filed this morning - re 210 Letter. (Jacobs, Karen) (Entered: 09/10/2019)
09/11/2019	212	REPORT AND RECOMMENDATION regarding claim construction. Please note that when filing Objections pursuant to Federal Rule of Civil Procedure 72 (b)(2), briefing consists solely of the Objections (no longer than ten (10) pages) and the Response to the Objections (no longer than ten (10) pages). No further briefing shall be permitted with respect to objections without leave of the Court. Objections to R&R due by 9/25/2019. Signed by Judge Christopher J. Burke on 9/11/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/11/2019)
09/11/2019	213	[SEALED] Letter to The Honorable Christopher J. Burke from Karen Jacobs regarding Defendants response to Guardant Health's letter [D.I. 206, 353) - re (206 in 1:17-cv-01616-LPS-CJB, 353 in 1:17-cv-01623-LPS-CJB) Letter. (Attachments: # 1 Exhibit 1-7)(Jacobs, Karen) (Attachment 1 replaced on 9/12/2019) (dlb). (Entered: 09/11/2019)
09/12/2019	214	REDACTED VERSION of (206 in 1:17-cv-01616-LPS-CJB, 353 in 1:17-cv-01623-LPS-CJB) Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibits A-C)(Farnan, Brian) (Entered: 09/12/2019)
09/12/2019		CORRECTING ENTRY: The exhibits PDF attached to the Letter at D.I. 213 has been replaced. (dlb) (Entered: 09/12/2019)
09/12/2019		Remark: The time for the Discovery Dispute Teleconference set for 9/16/2019 has been changed to commence at 4:00 P.M. The Court has set aside 45 minutes for the call. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/12/2019)
09/13/2019	215	[SEALED] Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Declaration from Third Party Illumina Inc. - re (362 in 1:17-cv-01623-LPS-CJB, 213 in 1:17-cv-01616-LPS-CJB) Letter,. (Attachments: # 1 Illumina Declaration)(Tigan, Jeremy) (Entered: 09/13/2019)
09/16/2019	216	Official Transcript of Discovery Dispute Teleconference held on 08/05/19 before Judge Christopher J. Burke. Court Reporter/Transcriber Heather M. Triozzi,Telephone number 302-573-6195. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/7/2019. Redacted Transcript Deadline set for 10/17/2019. Release of Transcript Restriction set for 12/16/2019. (Triozzi, Heather) (Entered: 09/16/2019)
09/16/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 9/16/2019 regarding Plaintiff's discovery dispute, (D.I. 203 in 17-1616-LPS-CJB; D.I. 349 in 17-1623-LPS-

		CJB). The Court took the matter under advisement. (Court Reporter Valerie Gunning. Clerk: M. Crawford) Appearances: B. Farnan, E. Reines, J. Constant for Plaintiff; J. Tigan, E. Marandett, M. Ives, R. Vallabhanen for Defendant Foundation Medicine, Inc.; J. Phillips, B. Zimmerman, S. Larson, J. Re for Defendant Personal Genome Diagnostics, Inc. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/16/2019)
09/17/2019	217	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Declaration of Dr. Helmy Eltoukhy. (Attachments: # 1 Attachment) (Farnan, Brian) (Entered: 09/17/2019)
09/17/2019	218	[SEALED] Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Defendants Response to Submission of Declaration of Dr. Eltoukhy. (Attachments: # 1 Exhibit 1)(Tigan, Jeremy) (Entered: 09/17/2019)
09/17/2019	219	[SEALED] Letter to The Honorable Christopher J. Burke from Karen Jacobs regarding Defendants response to Guardant Health's letter CORRECTED/AMENDED - re (362 in 1:17-cv-01623-LPS-CJB, 213 in 1:17-cv-01616-LPS-CJB) Letter,. (Attachments: # 1 Exhibits 1-8)(Jacobs, Karen) (Entered: 09/17/2019)
09/17/2019	220	REDACTED VERSION of 210 Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibits A-B)(Farnan, Brian) (Entered: 09/17/2019)
09/18/2019	221	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendants' September 17, 2019 Letter - re (367 in 1:17-cv-01623-LPS-CJB, 218 in 1:17-cv-01616-LPS-CJB) Letter. (Farnan, Brian) (Entered: 09/18/2019)
09/18/2019	222	ORAL ORDER: The Court hereby ORDERS as follows: (1) The Court has received the parties' supplemental letter briefs, (D.I. 217; D.I. 218; D.I. 221 in Civil Action No. 17-1616-LPS-CJB), filed without leave of Court following the September 16, 2019 discovery dispute teleconference regarding Plaintiff's discovery dispute motion, (D.I. 203 in Civil Action No. 17-1616-LPS-CJB). While the Court will accept these letters, the record on this motion is now closed, absent further leave of Court to file any additional letters regarding this motion. (2) No party may file a further supplemental letter regarding claim construction without leave of Court. Ordered by Judge Christopher J. Burke on 9/18/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/18/2019)
09/18/2019	223	REDACTED VERSION of (362 in 1:17-cv-01623-LPS-CJB, 213 in 1:17-cv-01616-LPS-CJB) Letter, *to The Honorable Christopher J. Burke from Karen Jacobs regarding Defendants response to Guardant Health's letter* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 1-8)(Tigan, Jeremy) (Entered: 09/18/2019)
09/18/2019	224	STIPULATION to Amend Scheduling Order by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 09/18/2019)
09/18/2019		SO ORDERED D.I. (224 in 1:17-cv-01616-LPS-CJB, 372 in 1:17-cv-01623-LPS-CJB) Stipulation to Amend Scheduling Order deadlines. Ordered by

		Judge Christopher J. Burke on 9/18/219. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/18/2019)
09/24/2019	225	REDACTED VERSION of (217 in 1:17-cv-01616-LPS-CJB, 366 in 1:17-cv-01623-LPS-CJB) Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 09/24/2019)
09/25/2019	226	NOTICE OF SERVICE of (i) Expert Reply Report of G. Cooper, Ph. D. and (ii) Expert Reply Report of S. L. Becker, Ph. D. filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 09/25/2019)
09/25/2019	227	NOTICE OF SERVICE of (1) Reply Expert Report of Michael L. Metzker, Ph.D., (2) Reply Report of Stacey Gabriel, Ph.D. Regarding Invalidity, and (3) Reply Expert Report of Thomas M. Wheeler, M.D. filed by Foundation Medicine, Inc..(Jacobs, Karen) (Entered: 09/25/2019)
09/25/2019	228	[SEALED] OBJECTIONS by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc. to (359 in 1:17-cv-01623-LPS-CJB) REPORT AND RECOMMENDATIONS. Please note that when filing Objections pursuant to Federal Rule of Civil Procedure 72(b)(2), briefing consists solely of the Objections (no longer than ten (10) pages) and the Response to the Objections (no longer than ten . (Attachments: # 1 Certification for Objections)(Phillips, John) (Entered: 09/25/2019)
09/27/2019	229	Letter to The Honorable Leonard P. Stark from John C. Phillips, Jr. regarding Report & Recommendation Docket Items - re (378 in 1:17-cv-01623-LPS-CJB) Objections,. (Phillips, John) (Entered: 09/27/2019)
09/30/2019	230	ORAL ORDER: Due to a scheduling conflict, the Court hereby ORDERS that the hearing on case dispositive and Daubert motions scheduled for January 24, 2020 is rescheduled to January 23, 2020 at 11:00a.m. in Courtroom 2A. Ordered by Judge Christopher J. Burke on 9/30/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/30/2019)
09/30/2019	231	REDACTED VERSION of (221 in 1:17-cv-01616-LPS-CJB, 369 in 1:17-cv-01623-LPS-CJB) Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 09/30/2019)
10/03/2019	232	MOTION for Pro Hac Vice Appearance of Attorney G. Mark Edgarton - filed by Foundation Medicine, Inc.. Motions referred to Christopher J. Burke.(Tigan, Jeremy) (Entered: 10/03/2019)
10/03/2019	233	REDACTED VERSION of (228 in 1:17-cv-01616-LPS-CJB, 378 in 1:17-cv-01623-LPS-CJB) Objections, by Foundation Medicine, Inc.. (Attachments: # 1 Certification for Objections)(Bilson, David) (Entered: 10/03/2019)
10/03/2019		SO ORDERED D.I. 232 MOTION for Pro Hac Vice Appearance of Attorney G. Mark Edgarton filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 10/3/2019. (dlb) (Entered: 10/03/2019)
10/04/2019	234	NOTICE to Take Deposition of Stephen Becker, Ph.D. on November 5, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 10/04/2019)
10/04/2019	235	

		NOTICE to Take Deposition of Gregory Cooper, Ph.D. on October 15, 2019 filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 10/04/2019)
10/07/2019	236	NOTICE OF SERVICE of Supplement to the Reply Expert Report of Michael L. Metzker, Ph.D. filed by Foundation Medicine, Inc..(Tigan, Jeremy) (Entered: 10/07/2019)
10/09/2019	237	[SEALED] RESPONSE TO OBJECTIONS by Guardant Health, Inc. re (228 in 1:17-cv-01616-LPS-CJB, 378 in 1:17-cv-01623-LPS-CJB) Objections, . (Farnan, Brian) (Entered: 10/09/2019)
10/09/2019	238	[SEALED] DECLARATION re (237 in 1:17-cv-01616-LPS-CJB, 387 in 1:17-cv-01623-LPS-CJB) Response to Objections *of Derek Walter* by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4)(Farnan, Brian) (Entered: 10/09/2019)
10/11/2019	239	REPORT AND RECOMMENDATION regarding claim construction. Please note that when filing Objections pursuant to Federal Rule of Civil Procedure 72 (b)(2), briefing consists solely of the Objections (no longer than ten (10) pages) and the Response to the Objections (no longer than ten (10) pages). No further briefing shall be permitted with respect to objections without leave of the Court. Objections to R&R due by 10/25/2019. Signed by Judge Christopher J. Burke on 10/11/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 10/11/2019)
10/14/2019	240	MOTION for Pro Hac Vice Appearance of Attorney Doug W. McClellan - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke. (Farnan, Brian) (Entered: 10/14/2019)
10/15/2019	241	MOTION to Strike Portions of the Expert Report of Julie Davis - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Michael) (Entered: 10/15/2019)
10/15/2019	242	[SEALED] Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Opening Letter Brief in Support of Motion to Strike - re 241 MOTION to Strike Portions of the Expert Report of Julie Davis . (Attachments: # 1 Certification, # 2 Exhibit A, # 3 Exhibit B, # 4 Exhibit C, # 5 Exhibit D, # 6 Exhibit E, # 7 Exhibit F, # 8 Exhibit G)(Farnan, Michael) (Entered: 10/15/2019)
10/16/2019		SO ORDERED D.I. 240 MOTION for Pro Hac Vice Appearance of Attorney Doug W. McClellan filed by Guardant Health, Inc.. Ordered by Judge Christopher J. Burke on 10/16/2019. (dlb) (Entered: 10/16/2019)
10/16/2019	243	REQUEST for Oral Argument by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 10/16/2019)
10/17/2019	244	REDACTED VERSION of (237 in 1:17-cv-01616-LPS-CJB, 387 in 1:17-cv-01623-LPS-CJB) Response to Objections by Guardant Health, Inc.. (Farnan, Brian) (Entered: 10/17/2019)
10/17/2019	245	REDACTED VERSION of (388 in 1:17-cv-01623-LPS-CJB, 238 in 1:17-cv-01616-LPS-CJB) Declaration, *of Derek Walter* by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-4)(Farnan, Brian) (Entered: 10/17/2019)

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PACER Login:	wg0135:2661645:0	**Client Code:**	51042.0004-f203
Description:	Docket Report	**Search Criteria:**	1:17-cv-01616-LPS-CJB Start date: 1/1/1970 End date: 10/21/2019
Billable Pages:	27	**Cost:**	2.70

CASREF,MEDIATION-CJB,PATENT

U.S. District Court
District of Delaware (Wilmington)
CIVIL DOCKET FOR CASE #: 1:17-cv-01623-LPS-CJB

Guardant Health, Inc. v. Personal Genome Diagnostics, Inc.
Assigned to: Judge Leonard P. Stark
Referred to: Judge Christopher J. Burke
Related Case: 1:17-cv-01616-LPS-CJB
Cause: 35:271 Patent Infringement

Date Filed: 11/09/2017
Jury Demand: Plaintiff
Nature of Suit: 830 Patent
Jurisdiction: Federal Question

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William R. Zimmerman
(See above for address)
ATTORNEY TO BE NOTICED

V.

Counter Defendant

Guardant Health, Inc. represented by **Joseph J. Farnan , Jr.**
(See above for address)
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Michael J. Farnan
(See above for address)
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Brian E. Farnan
(See above for address)
ATTORNEY TO BE NOTICED

Christopher M. Pistritto
(See above for address)
ATTORNEY TO BE NOTICED

Derek C. Walter
(See above for address)
ATTORNEY TO BE NOTICED

Edward R. Reines
(See above for address)
ATTORNEY TO BE NOTICED

Justin L. Constant
(See above for address)
ATTORNEY TO BE NOTICED

Trevor J. Quist
(See above for address)
TERMINATED: 08/17/2018
PRO HAC VICE

Counter Claimant

Personal Genome Diagnostics, Inc. represented by **John C. Phillips , Jr.**
(See above for address)
LEAD ATTORNEY
ATTORNEY TO BE NOTICED

Baraa Kahf
(See above for address)
ATTORNEY TO BE NOTICED

Danielle Nicole Petaja
(See above for address)
TERMINATED: 12/03/2018
ATTORNEY TO BE NOTICED

David A. Bilson
(See above for address)
ATTORNEY TO BE NOTICED

Gerard M. Clodomir
(See above for address)
TERMINATED: 04/13/2018
ATTORNEY TO BE NOTICED

Ioanna S. Bouris
(See above for address)
ATTORNEY TO BE NOTICED

James Darlington Taylor , Jr.
(See above for address)
TERMINATED: 12/12/2018
ATTORNEY TO BE NOTICED

Jeremiah S. Helm
(See above for address)
ATTORNEY TO BE NOTICED

Joseph R. Re
(See above for address)
ATTORNEY TO BE NOTICED

Karen Vogel Weil
(See above for address)
ATTORNEY TO BE NOTICED

Randall Shaw MacTough
(See above for address)
TERMINATED: 12/12/2018
ATTORNEY TO BE NOTICED

Stephen W. Larson
(See above for address)
ATTORNEY TO BE NOTICED

William R. Zimmerman
(See above for address)
ATTORNEY TO BE NOTICED

V.

Counter Defendant

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Justin L. Constant
(See above for address)
ATTORNEY TO BE NOTICED

Trevor J. Quist
(See above for address)
TERMINATED: 08/17/2018
PRO HAC VICE

Date Filed	#	Docket Text
11/09/2017	1	COMPLAINT - filed with Jury Demand against Personal Genome Diagnostics, Inc. - Magistrate Consent Notice to Pltf. (Filing fee $ 400, receipt number 0311-2264016.) - filed by Guardant Health, Inc. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Civil Cover Sheet)(rwc) (Entered: 11/13/2017)
11/09/2017	2	Notice, Consent and Referral forms re: U.S. Magistrate Judge jurisdiction. (rwc) (Entered: 11/13/2017)
11/09/2017	3	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) US 9,598,731 B2. (rwc) (Entered: 11/13/2017)
11/13/2017		Summons Issued with Magistrate Consent Notice attached as to Personal Genome Diagnostics, Inc. on 11/13/2017. Requesting party or attorney should pick up issued summons at the Help Desk, Room 4209, or call 302-573-6170 and ask the Clerk to mail the summons to them. (rwc) (Entered: 11/13/2017)
11/15/2017		Case Assigned to Judge Leonard P. Stark. Please include the initials of the Judge (LPS) after the case number on all documents filed. Associated Cases: 1:17-cv-01616-LPS, 1:17-cv-01623-LPS (rjb) (Entered: 11/15/2017)

11/21/2017	4	ORAL ORDER REFERRING CASE to Magistrate Judge Christopher J. Burke: IT IS HEREBY ORDERED that the above captioned case is referred to Magistrate Judge Christopher J. Burke to hear and resolve all pretrial matters, up to and including the resolution of case-dispositive motions, subject to 28 U.S.C. § 636(b) and any further Order of the Court; all subsequent filings in this action shall include the initials LPS-CJB after the case number. ORDERED by Judge Leonard P. Stark on 11/21/17. Associated Cases: 1:17-cv-01616-LPS, 1:17-cv-01623-LPS (ntl) (Entered: 11/21/2017)
11/21/2017	5	MOTION for Pro Hac Vice Appearance of Attorney Edward R. Reines and Derek C. Walter - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 11/21/2017)
11/27/2017		SO ORDERED D.I. 5 MOTION for Pro Hac Vice Appearance of Attorney Edward R. Reines and Derek C. Walter filed by Guardant Health, Inc.. Ordered by Judge Christopher J. Burke on 11/27/17. (mlc) (Entered: 11/27/2017)
11/28/2017	6	SUMMONS Returned Executed by Guardant Health, Inc.. Personal Genome Diagnostics, Inc. served on 11/28/2017, answer due 12/19/2017. (Farnan, Michael) (Entered: 11/28/2017)
12/15/2017	7	MOTION for Extension of Time to File Answer *move or otherwise respond* - filed by Personal Genome Diagnostics, Inc.. Motions referred to Christopher J. Burke.(Taylor, James) (Entered: 12/15/2017)
12/19/2017		SO ORDERED D.I. 7 MOTION for Extension of Time to File Answer *move or otherwise respond* filed by Personal Genome Diagnostics, Inc.. Ordered by Judge Christopher J. Burke on 12/19/2017. (mlc) (Entered: 12/19/2017)
12/20/2017		Pro Hac Vice Attorney Derek C. Walter,Edward R. Reines for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (crb) (Entered: 12/20/2017)
01/22/2018	8	MOTION to Dismiss for Failure to State a Claim - filed by Personal Genome Diagnostics, Inc.. Motions referred to Christopher J. Burke.(Clodomir, Gerard) (Entered: 01/22/2018)
01/22/2018	9	OPENING BRIEF in Support re 8 MOTION to Dismiss for Failure to State a Claim filed by Personal Genome Diagnostics, Inc..Answering Brief/Response due date per Local Rules is 2/5/2018. (Clodomir, Gerard) (Entered: 01/22/2018)
02/05/2018	10	First AMENDED COMPLAINT against Personal Genome Diagnostics, Inc.- filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10)(Farnan, Michael) (Entered: 02/05/2018)
02/05/2018	11	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) US 9,598,731 B2; US 9,834,822 B2; US 9,840,743 B2; . (Farnan, Michael) (Entered: 02/05/2018)
02/05/2018	12	RESPONSE to Motion re 8 MOTION to Dismiss for Failure to State a Claim filed by Guardant Health, Inc.. (Farnan, Michael) (Entered: 02/05/2018)

02/07/2018		ORAL ORDER: IT IS HEREBY ORDERED that the parties shall meet and confer and discuss, in person and/or by telephone, each of the matters listed on Chief Judge Stark's Case Management Checklist ("Checklist"). Within thirty (30) days from the date of this Order, the parties shall jointly file the following: (i) a copy of the "Checklist" indicating the names of Lead Counsel and Delaware Counsel for each party; (ii) a proposed Scheduling Order consistent with the Chief Judge Stark's Revised Patent Form Scheduling Order (with the exception that Paragraph (g) of the parties' proposed Scheduling Order shall be altered as follows: (a) the letter referenced in Paragraph (g)(ii) should be addressed to Judge Burke; (b) the time frames for the letters referenced in Paragraph (g)(iii) should be changed to 96 hours for the initial letter filed by the movant and 48 hours for the responsive letter filed by the opposing party; and (c) the parties should include an additional requirement that, after the Court has issued an order scheduling the discovery teleconference, the parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website); and (iii) a letter, not to exceed three pages, that contains the following: (a) a description of what this case is about; (b) the parties' positions regarding the disputes in the proposed Scheduling Order, and (c) a list of the three most significant topics (other than Scheduling Order disputes) discussed during the parties' review of the Checklist items, along with a brief description as to what was discussed as to those topics. Thereafter, the Court will schedule a Case Management Conference/Rule 16 Scheduling Conference to be held with Judge Burke. The Checklist and Revised Patent Form Scheduling Order can be found on this Court's website (www.ded.uscourts.gov/judge/chief-judge-leonard-p-stark). Ordered by Judge Christopher J. Burke on 2/7/2018. (dlb) (Entered: 02/07/2018)
02/15/2018	13	STIPULATION TO EXTEND TIME Defendant to move, answer or respond to Plaintiff's First Amended Complaint to March 21, 2018 - filed by Personal Genome Diagnostics, Inc.. (Taylor, James) (Entered: 02/15/2018)
02/15/2018		SO ORDERED D.I. 13 STIPULATION TO EXTEND TIME Defendant to move, answer or respond to Plaintiff's First Amended Complaint to March 21, 2018 filed by Personal Genome Diagnostics, Inc.. Ordered by Judge Christopher J. Burke on 2/15/2018. (mlc) (Entered: 02/15/2018)
02/26/2018	14	MOTION for Pro Hac Vice Appearance of Attorney Jessica Lu and Wayne Dennison - filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Certification, # 2 Certificatoin)Motions referred to Christopher J. Burke. (Taylor, James) (Entered: 02/26/2018)
03/08/2018	15	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s First Set of Interrogatories to Defendant (Nos. 1-5) and (ii) Guardant Health, Inc.'s First Set of Requests for Production of Documents and Things to Defendant (Nos. 1-62) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/08/2018)
03/09/2018	16	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Scheduling Materials. (Attachments: # 1 Proposed Scheduling Order, # 2 Case Management Checklist)(Farnan, Brian) (Entered: 03/09/2018)

03/12/2018		Order Setting Case Management/Scheduling Conference: A Case Management/Scheduling Conference is set for 3/26/2018 at 01:00 PM in Courtroom 2A before Judge Christopher J. Burke. Ordered by Judge Christopher J. Burke on 3/12/2018. (dlb) (Entered: 03/12/2018)
03/12/2018	17	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Combining Case Management Conferences. (Farnan, Michael) (Entered: 03/12/2018)
03/12/2018	18	Letter to The Honorable Christopher J. Burke from James D. Taylor regarding Scheduling of Case Management/Scheduling Conference - re 17 Letter. (Taylor, James) (Entered: 03/12/2018)
03/13/2018		ORAL ORDER: The Court, having reviewed the parties' recent letters (D.I. 19 in Civil Action No. 17-1616-LPS-CJB and D.I. 17-18 in Civil Action No. 17-1623-LPS-CJB), hereby ORDERS as follows: The Court will hold one in-person Case Management/Scheduling Conference in which it will discuss both cases, on March 26, 2018 at 1:00 p.m. in Chambers. To the extent that any counsel has a conflict and cannot attend that in-person conference, they should notify the Court promptly, and in any event no later than March 15, 2018. To the extent any party wishes to make a proposal as to what the contours of a consolidated schedule applying to both cases should look like, they may do so by letter filed no later than March 21, 2018 (and may attach a copy of the proposed schedule to such a letter). Otherwise, the Court will utilize the parties' previously-submitted materials in addressing outstanding disputes at the conference. Ordered by Judge Christopher J. Burke on 3/13/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) Modified on 3/13/2018 (dlb). (Entered: 03/13/2018)
03/21/2018		SO ORDERED D.I. 14 MOTION for Pro Hac Vice Appearance of Attorney Jessica Lu and Wayne Dennison filed by Personal Genome Diagnostics, Inc.. Ordered by Judge Christopher J. Burke on 3/21/2018. (dlb) (Entered: 03/21/2018)
03/22/2018	19	STIPULATION to File Second Amended Complaint by Guardant Health, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Farnan, Brian) (Entered: 03/22/2018)
03/23/2018		SO ORDERED D.I. 19 Stipulation to File Second Amended Complaint filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 3/23/2018. (dlb) (Entered: 03/23/2018)
03/23/2018	20	Second AMENDED COMPLAINT against Personal Genome Diagnostics, Inc.- filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12) (Farnan, Michael) (Entered: 03/23/2018)
03/23/2018	21	Report to the Commissioner of Patents and Trademarks for Patent/Trademark Number(s) US 9,598,731 B2; US 9,834,822 B2; US 9,840,743 B2; US 9,902,992 B2; . (Farnan, Michael) (Entered: 03/23/2018)
03/26/2018		

		Minute Entry for proceedings held before Judge Christopher J. Burke - Case Management/Scheduling Conference held on 3/26/2018. The Court heard the parties regarding any disputes and gave them key dates. Counsel shall confer regarding the rulings and submit one joint proposed schedule by April 2, 2018. (Court Reporter Brian Gaffigan) Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 03/26/2018)
03/27/2018	22	NOTICE OF SERVICE of Plaintiff's Identification of Accused Products, Asserted Patents, and Damages Model filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/27/2018)
03/29/2018	23	Official Transcript of Case Managment Conference held on March 26, 2018 before Judge Christopher J. Burke. Court Reporter Brian Gaffigan, Telephone (302) 573-6360. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 4/19/2018. Redacted Transcript Deadline set for 4/30/2018. Release of Transcript Restriction set for 6/27/2018. (bpg) (Entered: 03/29/2018)
04/02/2018	24	PROPOSED ORDER Proposed Scheduling Order by Guardant Health, Inc.. (Attachments: # 1 Letter to The Honorable Christopher J. Burke)(Farnan, Brian) (Entered: 04/02/2018)
04/04/2018	25	SCHEDULING ORDER: Joinder of Parties due by 1/4/2019. Amended Pleadings due by 1/4/2019. Fact Discovery completed by 4/12/2019. Status Report due by 2/8/2019. Dispositive Motions due by 10/4/2019. A Motion Hearing is set for 1/24/2020 at 11:00 AM in Courtroom 2A before Judge Christopher J. Burke Claim Construction Opening Brief due by 9/12/2018. Claim Construction Answering Brief due by 10/19/2018. Claim Construction Reply Brief due by 11/2/2018. A Markman Hearing is set for 12/14/2018 at 11:00 AM in Courtroom 2A before Judge Christopher J. Burke. A Pretrial Conference is set for 5/8/2020 at 09:00 AM in Courtroom 6B before Judge Leonard P. Stark. A Jury Trial is set for 5/18/2020 at 09:30 AM in Courtroom 6B before Judge Leonard P. Stark. A Jury Trial is set for 6/8/2020 at 09:30 AM in Courtroom 6B before Judge Leonard P. Stark.. Signed by Judge Christopher J. Burke on 4/3/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 04/04/2018)
04/06/2018	26	ANSWER to Amended Complaint, re: 20 Amended Complaint, with Jury Demand , COUNTERCLAIM *for Declaratory Judgment* against Guardant Health, Inc. by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 04/06/2018)
04/09/2018	27	NOTICE OF SERVICE of Guardant Health, Inc.'s Initial Disclosures filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/09/2018)
04/10/2018	28	NOTICE OF SERVICE of Initial Disclosures filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 04/10/2018)
04/13/2018	29	NOTICE OF SUBSTITUTION OF COUNSEL re Personal Genome Diagnostics, Inc.: Entry of appearance of attorney Danielle Nicole Petaja.

		Attorney Gerard M. Clodomir terminated. (Petaja, Danielle) (Entered: 04/13/2018)
04/13/2018	30	PROPOSED ORDER Proposed Protective Order by Guardant Health, Inc.. (Farnan, Brian) (Entered: 04/13/2018)
04/16/2018		SO ORDERED, re 30 Proposed Protective Order filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 4/16/2018. (dlb) (Entered: 04/16/2018)
04/16/2018	31	ANSWER to 26 Answer to Amended Complaint, Counterclaim by Guardant Health, Inc..(Farnan, Michael) (Entered: 04/16/2018)
04/20/2018	32	MOTION for Pro Hac Vice Appearance of Attorney Joseph Re, Karen Vogel Weil, William Zimmerman, Stephen Larson, Jeremiah Helm - filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Certification of Joseph Re, # 2 Certification of William Zimmerman, # 3 Certification of Stephen Larson, # 4 Certification of Karen Vogel Weil, # 5 Certification of Jeremiah Helm)Motions referred to Christopher J. Burke.(Taylor, James) (Entered: 04/20/2018)
04/23/2018	33	NOTICE OF SERVICE of Defendants answers and objections to Plaintiff's First Set of Interrogatories (Nos. 1-5) and First Set of Requests for Production (Nos. 1-62) filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 04/23/2018)
04/30/2018	34	NOTICE OF SERVICE of Core Technical Documents of Accused Products filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 04/30/2018)
05/03/2018	35	PROPOSED ORDER Proposed Stipulated Electronic Discovery Order by Guardant Health, Inc.. (Farnan, Brian) (Entered: 05/03/2018)
05/04/2018		SO ORDERED D.I. (35 in 1:17-cv-01623-LPS-CJB, 32 in 1:17-cv-01616-LPS-CJB) Proposed Stipulated Electronic Discovery Order filed by Guardant Health, Inc.. Ordered by Judge Christopher J. Burke on 5/4/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 05/04/2018)
05/07/2018	36	NOTICE OF SERVICE of Personal Genome's first set of Requests for Production of Documents and Things (1-137) filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 05/07/2018)
05/08/2018	37	NOTICE OF SERVICE of First Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. to Guardant Health, Inc. (1-9) filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Certificate of Service)(Taylor, James) (Entered: 05/08/2018)
05/17/2018		CASE REFERRED to Magistrate Judge Burke for Mediation. Please see Standing Order dated January 20, 2016, regarding disclosure of confidential ADR communications. A link to the standing order is provided here for your convenience at http://www.ded.uscourts.gov/general-orders/magistrate-judges-standing-order-adr-mediation (dlb) (Entered: 05/17/2018)
05/18/2018	38	

		NOTICE OF SERVICE of Personal Genome Diagnostics, Inc.'s Disclosures Pursuant to Stipulated Electronic Discovery Order filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 05/18/2018)
05/18/2018	39	NOTICE OF SERVICE of Plaintiff's ESI Disclosures filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 05/18/2018)
05/25/2018	40	NOTICE OF SERVICE of Guardant Health's Infringement Claim Charts for U.S. Patent Nos. 9,598,731; 9,840,743; 9,834,822; and 9,902,992 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 05/25/2018)
06/04/2018	41	MOTION for Pro Hac Vice Appearance of Attorney Trevor J. Quist - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 06/04/2018)
06/04/2018	42	NOTICE OF SERVICE of Guardant Health, Inc.'s Responses and Objections to Personal Genome Diagnostics, Inc.'s First Set of Requests for Production of Documents and Things (Nos. 1 - 137) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 06/04/2018)
06/06/2018		SO ORDERED D.I. 32 MOTION for Pro Hac Vice Appearance of Attorney Joseph Re, Karen Vogel Weil, William Zimmerman, Stephen Larson, Jeremiah Helm filed by Personal Genome Diagnostics, Inc. Ordered by Judge Christopher J. Burke on 6/6/2018. (dlb) (Entered: 06/06/2018)
06/06/2018		SO ORDERED D.I. (41 in 1:17-cv-01623-LPS-CJB, 38 in 1:17-cv-01616-LPS-CJB) MOTION for Pro Hac Vice Appearance of Attorney Trevor J. Quist filed by Guardant Health, Inc.. Ordered by Judge Christopher J. Burke on 6/6/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 06/06/2018)
06/07/2018	43	NOTICE OF SERVICE of Plaintiff's Responses and Objections to First Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 1-9) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 06/07/2018)
06/11/2018		Pro Hac Vice Attorney Stephen W. Larson,William R. Zimmerman for Personal Genome Diagnostics, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (fms) (Entered: 06/11/2018)
06/12/2018		Pro Hac Vice Attorney Karen Vogel Weil for Personal Genome Diagnostics, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (ceg) (Entered: 06/12/2018)
06/12/2018		Pro Hac Vice Attorney Joseph R. Re for Personal Genome Diagnostics, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (ceg) (Entered: 06/12/2018)
06/12/2018		Pro Hac Vice Attorney Trevor J. Quist for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers.

		Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(ceg) (Entered: 06/12/2018)
06/12/2018		Pro Hac Vice Attorney Jeremiah S. Helm for Personal Genome Diagnostics, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (crb) (Entered: 06/12/2018)
06/25/2018	44	NOTICE OF SERVICE of Initial Invalidity Contentions filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 06/25/2018)
07/02/2018	45	ORDER Setting Mediation Conference: A Telephone Conference is set for 7/30/2018 at 10:30 AM before Judge Christopher J. Burke to discuss ADR. Signed by Judge Christopher J. Burke on 7/2/2018. (dlb) (Entered: 07/02/2018)
08/03/2018	46	STIPULATION TO EXTEND TIME for the parties to submit a proposal regarding page limits on claim construction briefing to August 31, 2018 - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 08/03/2018)
08/03/2018		SO ORDERED D.I. (46 in 1:17-cv-01623-LPS-CJB, 42 in 1:17-cv-01616-LPS-CJB) STIPULATION TO EXTEND TIME for the parties to submit a proposal regarding page limits on claim construction briefing to August 31, 2018 filed by Foundation Medicine, Inc.. Ordered by Judge Christopher J. Burke on 8/3/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 08/03/2018)
08/03/2018	47	NOTICE OF SERVICE of Plaintiff Guardant Health, Inc.'s List of Claim Terms and Proposed Constructions filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 08/03/2018)
08/07/2018	48	NOTICE OF SERVICE of Defendants Preliminary Claim Construction Positions filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 08/07/2018)
08/10/2018	49	NOTICE OF SERVICE of Plaintiff's First Supplemental Response to Joint Interrogatory Nos. 3 & 9 of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 08/10/2018)
08/10/2018	50	NOTICE OF SERVICE of Supplemental Responses to Plaintiff's First Set of Interrogatories filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 08/10/2018)
08/14/2018	51	ORDER Setting Mediation Conference: A Mediation Conference is set for 9/11/2018 at 10:00 AM in Courtroom 2A before Judge Christopher J. Burke. Signed by Judge Christopher J. Burke on 8/14/2018. (dlb) (dlb). (Entered: 08/14/2018)
08/16/2018	52	NOTICE requesting Clerk to remove Trevor J. Quist as co-counsel.. (Farnan, Michael) (Entered: 08/16/2018)
08/31/2018	53	CLAIM Construction Chart by Guardant Health, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I, # 10 Exhibit J, # 11

		Exhibit K, # 12 Exhibit L, # 13 Exhibit M, # 14 Exhibit N, # 15 Exhibit O, # 16 Exhibit P, # 17 Exhibit Q, # 18 Exhibit R, # 19 Exhibit S, # 20 Exhibit T, # 21 Exhibit U, # 22 Exhibit V, # 23 Exhibit W, # 24 Exhibit X, # 25 Exhibit Y) (Farnan, Brian) (Entered: 08/31/2018)
08/31/2018	54	STIPULATION TO EXTEND TIME Claim Construction Briefing Limits to September 4, 2018 - filed by Guardant Health, Inc.. (Farnan, Michael) (Entered: 08/31/2018)
09/04/2018		SO ORDERED D.I. (54 in 1:17-cv-01623-LPS-CJB, 48 in 1:17-cv-01616-LPS-CJB) STIPULATION TO EXTEND TIME Claim Construction Briefing Limits to September 4, 2018 filed by Guardant Health, Inc..Ordered by Judge Christopher J. Burke on 9/4/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/04/2018)
09/04/2018	55	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Claim Construction Briefing Page Limits. (Farnan, Brian) (Entered: 09/04/2018)
09/05/2018		ORAL ORDER: The Court, having reviewed the parties' September 4, 2018 letter regarding their prospective proposals for claim construction briefing page limits, (D.I. (55 in 1:17-cv-01623-LPS-CJB, 49 in 1:17-cv-01616-LPS-CJB), HEREBY ORDERS as follows: (1) Plaintiff may have 20 pages for its opening brief and 15 pages for its reply brief.; and (2) Defendants may have either: (a) 25 pages for their answering brief and 10 pages for their sur-reply brief, or (b) 20 pages for their answering brief and 15 pages for their sur-reply brief. Ordered by Judge Christopher J. Burke on 9/5/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/05/2018)
09/21/2018	56	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Defendants' technology tutorial. (Tigan, Jeremy) (Entered: 09/21/2018)
09/21/2018	57	NOTICE OF SERVICE of Plaintiff's First Supplemental Response to Joint Interrogatory No. 6 of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 09/21/2018)
09/21/2018	58	NOTICE of filing the following Non-Paper material(s) in multi media format: two discs containing Plaintiff's Technology Tutorial. Original Non-paper material(s) to be filed with the Clerk's Office. Notice filed by Brian E. Farnan on behalf of Guardant Health, Inc. (Farnan, Brian) (Entered: 09/21/2018)
09/21/2018	59	[SEALED] CLAIM CONSTRUCTION OPENING BRIEF filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8)(Farnan, Brian) (Entered: 09/21/2018)
09/25/2018	60	Letter to The Honorable Christopher J. Burke from Danielle N. Petaja regarding Request for telephone conference. (Petaja, Danielle) (Entered: 09/25/2018)
09/26/2018	61	MULTI MEDIA DOCUMENT filed by Guardant Health, Inc. in the form of a CD containing Plaintiff's Technology Tutorial. Filing related to (52 in 1:17-cv-

		01616-LPS-CJB) Notice of Filing Multi Media Materials,. (Media on file in Clerk's Office). Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/26/2018)
09/26/2018	62	MULTI MEDIA DOCUMENT filed by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc. in the form of a CD containing Defendants' Technology Tutorial. Filing related to (50 in 1:17-cv-01616-LPS-CJB, 56 in 1:17-cv-01623-LPS-CJB) Letter (Media on file in Clerk's Office). Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/26/2018)
09/27/2018		ORAL ORDER: The Court has reviewed the parties' September 25, 2018 letter regarding a discovery dispute. (D.I. 60) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 25), will be followed with regard to this dispute. To that end: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference will be held on Monday, October 15, 2018 at 3:00 p.m.; (3) Not less than ninety-six (96) hours prior to the conference, excluding weekends and holidays, the party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. Not less than forty-eight (48) hours prior to the conference, excluding weekends and holidays, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; and (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing. Ordered by Judge Christopher J. Burke on 9/27/2018. (dlb) (Entered: 09/27/2018)
09/28/2018	63	REDACTED VERSION of (53 in 1:17-cv-01616-LPS-CJB) Claim Construction Opening Brief, (59 in 1:17-cv-01623-LPS-CJB) Claim Construction Opening Brief, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-8)(Farnan, Brian) (Entered: 09/28/2018)
10/01/2018	64	MOTION for Hearing re Order Setting Teleconference,,,,, - filed by Personal Genome Diagnostics, Inc.. Motions referred to Christopher J. Burke.(Petaja, Danielle) (Entered: 10/01/2018)
10/03/2018	65	NOTICE OF SERVICE of Guardant Health, Inc.'s Second Set of Requests for Production of Documents and Things to Defendant (Nos. 63-83) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 10/03/2018)
10/09/2018	66	Letter to The Honorable Christopher J. Burke from Danielle N. Petaja regarding issues in dispute-discovery teleconference 10/15/2018. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6)(Petaja, Danielle) (Entered: 10/09/2018)
10/10/2018		ORAL ORDER: The Court hereby ORDERS that by no later than November 30, 2018, the parties shall submit the joint letter required by Paragraph 14 of the Scheduling Order. (Civil Action No. 17-1616-LPS-CJB, D.I. 24 at 11; Civil Action No. 17-1623-LPS-CJB, D.I. 25 at 11) In addition to indicating (1)

		whether the parties request leave to present testimony at the claim construction hearing and (2) the amount of time the parties are requesting be allocated to them for the claim construction hearing, the parties' joint letter shall also indicate (3) the order in which the parties intend to present the claim terms at issue, including which side will present first for each term. Ordered by Judge Christopher J. Burke on 10/10/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 10/10/2018)
10/11/2018	67	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Response to Defendant's October 9, 2018 Letter - re 66 Letter,. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Farnan, Michael) (Entered: 10/11/2018)
10/15/2018		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery Teleconference held on 10/15/2018. The Court heard argument regarding Defendant's discovery dispute motion, (D.I. 64 , and will issue a short order. (Court Reporter Valerie Gunning. Clerk: M. Crawford) B. Farnan, D. Walter for Plaintiff; D. Petaja, S. Larson, J. Re for Defendant. (mlc) (Entered: 10/15/2018)
10/15/2018		ORAL ORDER: The Court, having reviewed Defendant's discovery dispute motion and related briefing, (D.I. 64 , 66, 67), and having discussed the disputes with the parties during today's discovery dispute teleconference, HEREBY ORDERS that Defendant's motion is DENIED. As to each of the four requests for production at issue, with respect to the specific or "core" responsive documents that Defendant called out in its letter, the Court does not have a sufficient basis to believe that Plaintiff has failed to produce any such documents that are in its possession, custody or control. Ordered by Judge Christopher J. Burke on 10/15/2018. (mlc) (Entered: 10/15/2018)
10/19/2018	68	CLAIM CONSTRUCTION ANSWERING BRIEF re 59 Claim Construction Opening Brief, filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Exhibits 1-4)(Tigan, Jeremy) (Entered: 10/19/2018)
10/19/2018	69	DECLARATION re (58 in 1:17-cv-01616-LPS-CJB) Claim Construction Answering Brief, (68 in 1:17-cv-01623-LPS-CJB) Claim Construction Answering Brief *(Stacey Gabriel)* by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 10/19/2018)
10/19/2018	70	STATEMENT re (61 in 1:17-cv-01623-LPS-CJB, 54 in 1:17-cv-01616-LPS-CJB) Multi Media Document, *[Defendants' Comments on Plaintiff's Technology Tutorial]* by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 10/19/2018)
10/19/2018	71	STATEMENT *[Plaintiff's Comments On Defendants' Technology Tutorial]* by Guardant Health, Inc.. (Farnan, Brian) (Entered: 10/19/2018)
11/02/2018	72	CLAIM CONSTRUCTION REPLY BRIEF re 68 Claim Construction Answering Brief filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 11/02/2018)
11/05/2018	73	NOTICE OF SERVICE of Personal Genome Diagnostics, Inc.'s Responses and Objections to Guardant Health, Inc.'s Second Set of Requests for Production

		(Nos. 63-83) filed by Personal Genome Diagnostics, Inc..(Taylor, James) (Entered: 11/05/2018)
11/16/2018	74	CLAIM CONSTRUCTION SURREPLY BRIEF re 72 Claim Construction Reply Brief filed by Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 11/16/2018)
11/27/2018	75	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding courtesy copies of the slides from Defendants' Technical Tutorial - re (50 in 1:17-cv-01616-LPS-CJB, 56 in 1:17-cv-01623-LPS-CJB) Letter. (Attachments: # 1 Defendants' Tutorial Presentation)(Tigan, Jeremy) (Entered: 11/27/2018)
11/30/2018	76	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Claim Construction Hearing Process. (Farnan, Michael) (Entered: 11/30/2018)
12/03/2018	77	NOTICE OF SUBSTITUTION OF COUNSEL re Personal Genome Diagnostics, Inc.: Entry of appearance of attorney Randall Shaw MacTough. Attorney Danielle N. Petaja terminated. (MacTough, Randall) (Entered: 12/03/2018)
12/06/2018	78	ORDER Setting Mediation Conference: A Telephone Conference is set for 1/14/2019 at 11:00 AM before Judge Christopher J. Burke. Signed by Judge Christopher J. Burke on 17-1623. (dlb) (Entered: 12/06/2018)
12/11/2018		ORAL ORDER: The Court, having reviewed the parties' joint letter regarding the upcoming claim construction hearing, (D.I. 66 in Civil Action No. 17-1616-LPS-CJB; D.I. 76 in Civil Action No. 17-1623-LPS-CJB), HEREBY ORDERS as follows: (1) The Court adopts the parties' proposal that 3 hours be allocated for the hearing, split evenly between Plaintiff and Defendants.; (2) The Court will hear argument on the terms in the order proposed by Defendants, for substantially the reasons offered by Defendants, (id. at 2).; and (3) In light of the dispute as to which side will present first, the Court will defer to the patent owner. (Id.) Plaintiff will present first for each term, followed by Defendants (with Plaintiff and then Defendants thereafter provided opportunity for brief rebuttal.) Ordered by Judge Christopher J. Burke on 12/3/2018. (dlb) (Entered: 12/11/2018)
12/12/2018	79	NOTICE OF SUBSTITUTION OF COUNSEL re Personal Genome Diagnostics, Inc.: Entry of appearance of attorney John C. Phillips, Jr. Attorney James D. Taylor and Randall S. MacTough terminated. (Phillips, John) (Entered: 12/12/2018)
12/13/2018	80	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Request for Discovery Teleconference. (Farnan, Michael) (Entered: 12/13/2018)
12/13/2018		ORAL ORDER: The Court has reviewed the parties' December 13, 2018 letter requesting a discovery teleconference regarding 2 discovery disputes. (D.I.80) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 25), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab

		of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is scheduled for January 14, 2019 at 3:00 p.m.; (3) By no later than December 18, 2018, the party seeking relief shall file with the Court a letter, not to exceed four (4) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than December 21, 2018, any party opposing the application for relief may file a letter, not to exceed four (4) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 12/13/2018. (dlb) (Entered: 12/13/2018)
12/14/2018	81	Joint MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 12/14/2018)
12/14/2018	82	NOTICE of Appearance by David A. Bilson on behalf of Personal Genome Diagnostics, Inc. (Bilson, David) (Entered: 12/14/2018)
12/14/2018		Minute Entry for proceedings held before Judge Christopher J. Burke - Markman Hearing held on 12/14/2018. The Court took the matter under advisement. With respect to the newly raised argument relating to the dependent claim, Defendants may file a letter brief of no more than 2 single-spaced pages by no later than December 21, 2018. (Court Reporter John Donnelly (Veritext). Clerk: M. Crawford) Appearances: B. Farnan, D. Walter, S. Chi, E. Reines for Plaintiff; J. Tigan, E. Marandett, M. Barrett for Foundation Medicine, Inc.; D. Bilson, J. Re, S. Larson, B. Zimmerman, J. Helm for Defendant Personal Genome Diagnostics, Inc. and Personal Genome Diagnostics, Inc. Associated Cases: 1:17-cv-01623-LPS-CJB, 1:17-cv-01616-LPS-CJB(mlc) (Entered: 12/14/2018)
12/17/2018		ORAL ORDER: The Court HEREBY ORDERS as follows: During the December 14, 2018 Markman hearing, the parties discussed the deposition testimony of Defendants' expert Dr. Gabriel, which Dr. Gabriel provided in the inter partes review proceeding that followed claim construction briefing in this case. By no later than December 21, 2018, Plaintiff may submit a supplemental letter brief of no more than 3 single-spaced pages addressing this testimony and its impact on claim construction in this matter. By no later than January 2, 2019, Defendants may file a responsive supplemental letter brief of no more than 3 single-spaced pages on the same topic. Ordered by Judge Christopher J. Burke on 12/17/2018. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 12/17/2018)
12/18/2018	83	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7)(Farnan, Brian) (Entered: 12/18/2018)
12/21/2018	84	Letter to The Honorable Christopher J. Burke from David A. Bilson regarding new argument raised by Plaintiff at Markman hearing. (Bilson, David) (Entered: 12/21/2018)

12/21/2018	85	Official Transcript of Claim Construction Hearing held on December 14, 2018 before Judge Christopher J. Burke. Court Reporter John P. Donnelley of Veritext Reporting, Telephone (302) 571-0510. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 1/11/2019. Redacted Transcript Deadline set for 1/22/2019. Release of Transcript Restriction set for 3/21/2019. (bpg) (Entered: 12/21/2018)
12/21/2018	86	STIPULATION TO EXTEND TIME to File Supplemental Responsive Letter Brief re: Gabriel Testimony to January 4, 2019 - filed by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 12/21/2018)
12/21/2018		SO ORDERED D.I. (86 in 1:17-cv-01623-LPS-CJB, 69 in 1:17-cv-01616-LPS-CJB) STIPULATION TO EXTEND TIME to File Supplemental Responsive Letter Brief re: Gabriel Testimony to January 4, 2019 filed by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc. Ordered by Judge Christopher J. Burke on 12/21/2018. Associated Cases: 1:17-cv-01623-LPS-CJB, 1:17-cv-01616-LPS-CJB(mlc) (Entered: 12/21/2018)
12/21/2018	87	Letter to The Honorable Christopher J. Burke from David A. Bilson regarding PGDx's Response to Guardant's Motion to Compel (D.I. 83). (Attachments: # 1 Exhibits A-F)(Bilson, David) (Entered: 12/21/2018)
12/21/2018	88	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Claim Construction Expert Testimony. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3)(Farnan, Michael) (Entered: 12/21/2018)
01/03/2019	89	ORDER regarding D.I. 81 Joint MOTION for Teleconference to Resolve Discovery Dispute filed by Guardant Health, Inc., ORDER Cancelling Deadline. Signed by Judge Christopher J. Burke on 1/3/2019. (mlc) (Entered: 01/03/2019)
01/04/2019	90	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Response to Guardant's December 21, 2018 Letter. (Tigan, Jeremy) (Entered: 01/04/2019)
01/07/2019		CORRECTING ENTRY: Transcript filed at D.I. 91 was removed from the docket (duplicate of D.I. 85). (ntl) (Entered: 01/07/2019)
01/07/2019		REDACTION NOTICE: In accordance with section G of the Administrative Procedures Governing Filing and Service by Electronic Means, redacted versions of sealed documents shall be filed electronically within 7 days of the filing of the sealed document. The records of this case do not reflect the filing of a redacted version of D.I. No. 83. (mlc) (Entered: 01/07/2019)
01/08/2019	91	REDACTED VERSION of 83 Letter, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-7)(Farnan, Brian) (Entered: 01/08/2019)
01/09/2019	92	NOTICE OF SERVICE of Plaintiff's Supplemental Identification of Accused Products filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/09/2019)

01/10/2019	93	[SEALED] DECLARATION re 89 Order, Order Cancelling Deadline *of Derek Walter Regarding Court's Order on Source Code* by Guardant Health, Inc.. (Attachments: # 1 Letter to The Honorable Christopher J. Burke)(Farnan, Michael) (Entered: 01/10/2019)
01/11/2019		ORAL ORDER: Due to a scheduling conflict, the Court HEREBY ORDERS that the ADR teleconference scheduled for January 14, 2019 at 11:00 a.m. is cancelled. Ordered by Judge Christopher J. Burke on 1/11/2019. (mlc) (Entered: 01/11/2019)
01/11/2019	94	NOTICE of Subpoena (Chronix Biomedical, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/11/2019	95	NOTICE of Subpoena (Cynvenio Biosystems, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/11/2019	96	NOTICE of Subpoena (Natera, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/11/2019	97	NOTICE of Subpoena (Sequenom, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/11/2019	98	NOTICE of Subpoena (Verinata Health, Inc.) by Foundation Medicine, Inc. (Tigan, Jeremy) (Entered: 01/11/2019)
01/16/2019		ORAL ORDER: The Court, having reviewed Plaintiff's declaration, (D.I. 93), accepts the representations therein, and finds that Plaintiff has now met its burden to establish that Defendant should timely produce the full set of printouts of portions of Defendant's source code that have been previously identified by Plaintiff, (D.I. 89 at 1-2). Ordered by Judge Christopher J. Burke on 1/16/2019. (dlb) (Entered: 01/16/2019)
01/17/2019	99	REDACTED VERSION of 93 Declaration by Guardant Health, Inc.. (Attachments: # 1 Letter to The Honorable Christopher J. Burke)(Farnan, Michael) (Entered: 01/17/2019)
01/18/2019	100	NOTICE to Take Deposition of Travis Clark on 3/1/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	101	NOTICE to Take Deposition of Matt Franklin on 3/6/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	102	NOTICE to Take Deposition of Mark Kennedy on 3/5/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	103	NOTICE to Take Deposition of Doron Lipson on 3/8/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	104	NOTICE to Take Deposition of Geoff Otto on 3/11/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	105	NOTICE to Take Deposition of Jeff Palmer on 3/4/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	106	

		NOTICE to Take Deposition of John Truesdell on 3/7/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	107	NOTICE to Take Deposition of Personal Genome Diagnostics, Inc. on 3/22/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/18/2019)
01/18/2019	108	NOTICE to Take Deposition of Justin Odegaard on March 7, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	109	NOTICE to Take Deposition of Amirali Talasaz on March 20-21, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	110	NOTICE to Take Deposition of Mark Jacobstein on February 19, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	111	NOTICE to Take Deposition of Helmy Eltoukhy on March 25-26, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	112	NOTICE to Take Deposition of Stefanie Mortimer on February 11-12, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	113	NOTICE to Take Deposition of Lai Mun Siew on February 21, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	114	NOTICE to Take Deposition of Derek Bertocci on March 12, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	115	NOTICE to Take Deposition of Rick Lanman on March 5, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	116	NOTICE to Take Deposition of Bill Getty on March 1, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/18/2019	117	NOTICE to Take Deposition of Michael Wiley on February 25, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 01/18/2019)
01/24/2019	118	NOTICE OF SERVICE of Plaintiff's Second Supplemental Identification of Accused Products filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 01/24/2019)
01/25/2019	119	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Request for Discovery Teleconference. (Farnan, Michael) (Entered: 01/25/2019)
01/28/2019		ORAL ORDER: The Court has reviewed the parties' January 25, 2019 letter requesting a discovery teleconference regarding 1 discovery dispute. (D.I. 119) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 25), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is scheduled for February 5, 2019 at 4:00 p.m.; (3) By no later than January 30, 2019, the party seeking relief shall file with the Court a letter, not to exceed four (4) pages, in no less than 12-point font, outlining the issues

		in dispute and its position on those issues. By no later than February 1, 2019, any party opposing the application for relief may file a letter, not to exceed four (4) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference. (dlb) (Entered: 01/28/2019)
01/28/2019	120	Joint MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 01/28/2019)
01/28/2019	121	NOTICE requesting Clerk to remove Jessica T. Lu and Wayne F. Dennison as co-counsel. Reason for request: No Longer Affiliated with the case. (Bilson, David) (Entered: 01/28/2019)
01/30/2019	122	NOTICE OF SERVICE of Second Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. to Guardant Health, Inc. (10-12) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 01/30/2019)
01/30/2019	123	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s First Set of Interrogatories to Guardant Health, Inc. (1-2) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 01/30/2019)
01/30/2019	124	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9)(Farnan, Brian) (Entered: 01/30/2019)
02/01/2019	125	[SEALED] Letter to the Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Letter responding to plaintiff's January 31, 2019 discovery dispute letter. (Attachments: # 1 Exhibit A-C)(Phillips, John) (Entered: 02/01/2019)
02/01/2019	126	[SEALED] DECLARATION re 125 Letter *Declaration Of Mark Sausen In Support Of PGDxs Opposition To Guardants Motion To Compel* by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 02/01/2019)
02/04/2019	127	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Oral Argument - re 126 Declaration, 125 Letter. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Farnan, Michael) (Entered: 02/04/2019)
02/04/2019	128	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding response to Guardant's February 4, 2019 letter. (Phillips, John) (Entered: 02/04/2019)
02/05/2019	129	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Supplemental Claim Construction Brief Given Defendant's Recent IPR Petitions. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E)(Farnan, Brian) (Entered: 02/05/2019)
02/05/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 2/5/2019. The Court heard argument

		regarding Plaintiff's discovery dispute motion, (D.I. 120), and will issue an order. (Court Reporter John Donnelly (Veritext). Clerk: M. Crawford) Appearances: B. Farnan, E. Reines, D. Walter for Plaintiff; J. Phillips, S. Larson, J. Re for Defendant. (mlc) (Entered: 02/05/2019)
02/06/2019		ORAL ORDER: The Court, having reviewed Plaintiff's February 5, 2019 letter, (Civil Action No. 17-1616-LPS-CJB, D.I. 98; Civil Action No. 17-1623-LPS-CJB, D.I. 129), HEREBY ORDERS that Plaintiff's request is GRANTED as follows: (1) By no later than February 13, 2019, Plaintiff shall file a supplemental claim construction brief of no more than 5 double-spaced pages to address Defendant Foundation Medicine, Inc.'s recent inter partes review petitions directed to three of the asserted patents; and (2) By no later than February 20, 2019, Defendants may file a joint responsive supplemental claim construction brief of no more than 5 double-spaced pages. Ordered by Judge Christopher J. Burke on 2/6/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 02/06/2019)
02/07/2019		ORAL ORDER: The Court, having reviewed Plaintiff's discovery dispute motion, (D.I. 120), and the parties' letter briefs relating thereto, (D.I. 124; D.I. 125; D.I. 127; D.I. 128), and having heard argument on February 5, 2019, hereby GRANTS Plaintiff's motion as follows. (1) Earlier in the case, the Court ruled that Plaintiff had not sufficiently demonstrated why (pursuant to the requirements of the parties' ESI Order) it had satisfied its obligations, such that Defendant should then have been required to utilize Plaintiff's three additional proposed search terms. (D.I. 89 at 3) But in making that ruling, the Court did not intend to prohibit Plaintiff from ever seeking to make such a showing. (2) In the interval, Plaintiff has propounded a revised set of three search terms, (D.I. 124, ex. 2), which are more narrow than its earlier-proposed terms and do address at least some of Defendant's prior objections to the breadth of the originally-proposed terms. (3) The three revised terms will return relevant evidence, and Defendant has not provided data suggesting that the new terms would pose an undue burden on it, pursuant to Fed. R. Civ. P. 26(b). (4) Although Plaintiff should have made such efforts to engage with Defendant's objections regarding the terms earlier in the case schedule, it is not too late for these searches to be performed. (D.I. 124 at 4) This outcome is also a fair one, as it does seem that the ESI Order contemplates that (as long as Plaintiff follows the rules set out in the ESI Order), Plaintiff would be able to propound at least three search terms of its own to Defendant and receive related search results. (5) With respect to Defendant's argument that producing documents generated by these searches would effectively be an end-run around Defendant's objections to various Requests for Production of Documents ("RFPs"), the Court is not in a position to find that otherwise responsive documents should be withheld from production on this ground (i.e., because they solely relate to an RFP that has been objected to). (6) Accordingly, Plaintiff's motion is GRANTED. In a timely fashion, Defendant shall search for and produce relevant responsive documents containing the three revised keywords propounded by Plaintiff. To the extent that, following its search, Defendant asserts that certain sub-categories of otherwise responsive documents should not be produced in light of its pending objections to RFPs, it may raise the issue with the Court pursuant to the Court's discovery dispute

		procedures (if the parties cannot resolve the issue after meeting and conferring). (7) Lastly, with respect to the issue relating to the Elio Plasma Resolve product ("elio") referenced in the parties' letter briefs, (D.I. 124 at 3; D.I. 125 at 4; D.I. 128 at 1), by no later than February 14, 2019, the parties shall meet and confer to try to reach agreement as to whether or not elio is an accused product in this case. Ordered by Judge Christopher J. Burke on 2/7/2019. (mlc) (Entered: 02/07/2019)
02/07/2019	130	NOTICE to Take Deposition of Guardant Health, Inc. Pursuant to Fed. R. Civ. P. 30(b)(6) on March 25, 2019 filed by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 02/07/2019)
02/08/2019	131	Joint STATUS REPORT by Guardant Health, Inc.. (Farnan, Brian) (Entered: 02/08/2019)
02/11/2019	132	REDACTED VERSION of 125 Letter by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 02/11/2019)
02/11/2019	133	REDACTED VERSION of 126 Declaration by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 02/11/2019)
02/11/2019	134	REDACTED VERSION of 127 Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibits A-B)(Farnan, Brian) (Entered: 02/11/2019)
02/12/2019	135	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s Objections to Guardant Health, Inc.'s Notice of Deposition Pursuant to Fed. R. Civ. P. 30(b)(6) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 02/12/2019)
02/13/2019	136	STATEMENT *Plaintiff's Supplemental Claim Construction Brief* by Guardant Health, Inc.. (Attachments: # 1 Exhibit 9)(Farnan, Brian) (Entered: 02/13/2019)
02/14/2019	137	NOTICE OF SERVICE of Guardant Health, Inc.'s First Amended Infringement Contentions filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 02/14/2019)
02/15/2019	138	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s Supplemental Identification of Prior Art filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 02/15/2019)
02/20/2019	139	STATEMENT re (136 in 1:17-cv-01623-LPS-CJB, 101 in 1:17-cv-01616-LPS-CJB) Statement *Defendants' Supplemental Responsive Markman Brief* by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc.. (Tigan, Jeremy) (Entered: 02/20/2019)
02/22/2019	140	STIPULATION TO EXTEND TIME to Amend/Supplement Pleadings to April 26, 2019 and May 3, 2019 - filed by Guardant Health, Inc.. (Farnan, Michael) (Entered: 02/22/2019)
02/25/2019		SO ORDERED D.I. 140 STIPULATION TO EXTEND TIME to Amend/Supplement Pleadings to April 26, 2019 and May 3, 2019 filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 2/25/2019. (dlb) (Entered: 02/25/2019)

02/27/2019	141	MOTION for Pro Hac Vice Appearance of Attorney Christopher M. Pistritto and Justin L. Constant - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 02/27/2019)
02/27/2019		SO ORDERED D.I. (105 in 1:17-cv-01616-LPS-CJB, 141 in 1:17-cv-01623-LPS-CJB) MOTION for Pro Hac Vice Appearance of Attorney Christopher M. Pistritto and Justin L. Constant filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 2/27/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 02/27/2019)
02/28/2019	142	NOTICE of Defendant Personal Genome Diagnostics, Inc.'s Notice of Third Party Subpoenas to Jeffrey J. Seidel by Personal Genome Diagnostics, Inc. (Phillips, John) (Entered: 02/28/2019)
02/28/2019	143	NOTICE of Defendant Personal Genome Diagnostics, Inc.'s Notice of Third Party Subpoena to Wilson, Sonsini, Goodrich & Rosati by Personal Genome Diagnostics, Inc. (Phillips, John) (Entered: 02/28/2019)
02/28/2019	144	NOTICE of Defendant Personal Genome Diagnostics, Inc.'s Notice of Third Party Subpoenas to Vern Norviel by Personal Genome Diagnostics, Inc. (Phillips, John) (Entered: 02/28/2019)
03/01/2019	145	NOTICE OF SERVICE of Final Infringement Contentions filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/01/2019)
03/01/2019	146	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s Responses and Objections to Personal Genome Diagnostics, Inc.'s First Set of Interrogatories (Nos. 1 - 2) and (ii) Plaintiff's Responses and Objections to Second Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 10-12) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/01/2019)
03/04/2019	147	NOTICE OF SERVICE of Plaintiff Guardant Health, Inc.'s Responses and Objections to Personal Genome Diagnostics, Inc.'s Notice of Deposition Pursuant To Fed. R. Civ. P. 30(b)(6) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/04/2019)
03/05/2019	148	SUBPOENA Returned Executed as to Jeffrey J. Seidel on March 4, 2019 (Phillips, John) (Entered: 03/05/2019)
03/05/2019	149	SUBPOENA Returned Executed as to Jeffrey J. Seidel on March 4, 2019 (Phillips, John) (Entered: 03/05/2019)
03/06/2019		Pro Hac Vice Attorney Justin L. Constant and Christopher M. Pistritto for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (ceg) (Entered: 03/06/2019)
03/06/2019	150	Official Transcript of Case Management Conference held on February 5, 2019 before Judge Christopher J. Burke. Court Reporter/Transcriber John Donnelly of Veritext, Telephone (302) 571-0510. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 3/27/2019. Redacted

		Transcript Deadline set for 4/8/2019. Release of Transcript Restriction set for 6/4/2019. (bpg) (Entered: 03/06/2019)
03/12/2019	151	SUBPOENA Returned Executed as to Wilson Sonsini Goodrich & Rosati on March 1, 2019 (Bilson, David) (Entered: 03/12/2019)
03/12/2019	152	SUBPOENA Returned Executed as to Vern Norviel on March 1, 2019 (Bilson, David) (Entered: 03/12/2019)
03/12/2019	153	SUBPOENA Returned Executed as to Vern Norviel [Documents] on March 1, 2019 (Bilson, David) (Entered: 03/12/2019)
03/12/2019	154	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding IPR POPR. (Attachments: # 1 Exhibit 1)(Phillips, John) (Entered: 03/12/2019)
03/12/2019	155	NOTICE to Take Deposition of Samuel Angiuoli on 3/29/2019 filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/12/2019)
03/12/2019	156	Joint STIPULATION TO EXTEND TIME for the completion of fact depositions; and other non-expert discovery to May 1, 2019 and May 15, 2019 respectively - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 03/12/2019)
03/13/2019		SO ORDERED D.I. (113 in 1:17-cv-01616-LPS-CJB, 156 in 1:17-cv-01623-LPS-CJB) Joint STIPULATION TO EXTEND TIME for the completion of fact depositions; and other non-expert discovery to May 1, 2019 and May 15, 2019 respectively filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 3/13/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 03/13/2019)
03/13/2019	157	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendant's March 12, 2019 - re 154 Letter. (Farnan, Brian) (Entered: 03/13/2019)
03/13/2019	158	ORAL ORDER: The Court, having reviewed Defendant's March 12, 2019 letter, (D.I. 154), and Plaintiff's March 13, 2019 letter, (D.I. 157), HEREBY ORDERS that: (1) By no later than March 20, 2019, Defendant shall file a supplemental claim construction brief of no more than 1 single-spaced page to address Plaintiff's recent Patent Owner Preliminary Response in the inter partes review proceeding directed to one of the asserted patents; and (2) By no later than March 27, 2019, Plaintiff may file a responsive supplemental claim construction brief of no more than 1 single-spaced page. Ordered by Judge Christopher J. Burke on 3/13/2019. (dlb) (Entered: 03/13/2019)
03/13/2019	159	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s Supplemental Initial Disclosures filed by Personal Genome Diagnostics, Inc.. (Bilson, David) (Entered: 03/13/2019)
03/20/2019	160	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding requesting discovery dispute teleconference. (Phillips, John) (Entered: 03/20/2019)
03/20/2019	161	

		ORAL ORDER: The Court has reviewed the parties' March 20, 2019 letter requesting a discovery teleconference regarding 3 discovery disputes. (D.I. 160) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 25), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is scheduled for April 1, 2019 at 3:00 p.m.; (3) By no later than March 25, 2019, the party seeking relief shall file with the Court a letter, not to exceed four (4) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than March 28, 2019, any party opposing the application for relief may file a letter, not to exceed four (4) pages, in no less than 12-point font, outlining that party (s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the disputes prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 3/20/2019. (dlb) (Entered: 03/20/2019)
03/20/2019	162	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Defendant's Supplemental Claim Construction Brief - re 158 Oral Order,,. (Attachments: # 1 Exhibit 1)(Phillips, John) (Entered: 03/20/2019)
03/21/2019	163	NOTICE to Take Deposition of Andrew Georgiadis on 4/23/2019 filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/21/2019)
03/21/2019	164	Joint MOTION for Teleconference to Resolve Discovery Dispute - filed by Personal Genome Diagnostics, Inc.. Motions referred to Christopher J. Burke. (Bilson, David) (Entered: 03/21/2019)
03/21/2019	165	MOTION for Pro Hac Vice Appearance of Attorney Ioanna S. Bouris - filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Certification of Ioanna S. Bouris)Motions referred to Christopher J. Burke.(Bilson, David) (Entered: 03/21/2019)
03/22/2019	166	MOTION for Pro Hac Vice Appearance of Attorney Baraa Kahf - filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Certification of Baraa Kahf)Motions referred to Christopher J. Burke.(Bilson, David) (Entered: 03/22/2019)
03/22/2019	167	NOTICE to Take Deposition of Mark Sausen, Ph.D. on 3/27/2019 (Amended) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/22/2019)
03/22/2019	168	NOTICE to Take Deposition of William Stevens on 4/5/2019 (Amended) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/22/2019)
03/25/2019	169	NOTICE to Take Deposition of William Stevens on 4/5/2019 (Second Amended) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/25/2019)
03/25/2019	170	NOTICE to Take Deposition of Mark Sausen, Ph.D. on 3/27/2019 (Second Amended) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 03/25/2019)

03/25/2019	171	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Discovery Dispute. (Attachments: # 1 Exhibit 1 - 15) (Phillips, John) (Entered: 03/25/2019)
03/25/2019	172	[SEALED] Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8)(Farnan, Michael) (Entered: 03/25/2019)
03/27/2019	173	(SEALED) Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Plaintiff's Responsive Supplemental Claim Construction Brief - re 162 Letter. (Attachments: # 1 Exhibit 1)(Farnan, Brian) Modified on 3/28/2019 (dlb). (Entered: 03/27/2019)
03/28/2019		SO ORDERED D.I. 165 MOTION for Pro Hac Vice Appearance of Attorney Ioanna S. Bouris filed by Personal Genome Diagnostics, Inc., 166 MOTION for Pro Hac Vice Appearance of Attorney Baraa Kahf filed by Personal Genome Diagnostics, Inc. Ordered by Judge Christopher J. Burke on 3/28/2019. (dlb) (Entered: 03/28/2019)
03/28/2019	174	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s First Set of Common Interrogatories to Defendants (Nos. 1-8); (ii) Guardant Health, Inc.'s First Set of Requests for Admission by Defendant (Nos. 1-21); (iii) Guardant Health, Inc.'s Second Set of Interrogatories to Defendant (Nos. 6-9); and (iv) Guardant Health, Inc.'s Third Set of Requests for Production of Documents and Things to Defendant (Nos. 84 -89) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 03/28/2019)
03/28/2019		CORRECTING ENTRY: Document filed at D.I. 173 has been placed under seal at the request of the filer. (dlb) (Entered: 03/28/2019)
03/28/2019	175	[SEALED] Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Response to Defendant's March 25, 2019 Letter - re 171 Letter. (Attachments: # 1 Exhibit 1)(Farnan, Michael) (Entered: 03/28/2019)
03/28/2019	176	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding response to plaintiff's March 25, 2019 discovery dispute letter - re 172 Letter,. (Attachments: # 1 Exhibit A - I)(Phillips, John) (Entered: 03/28/2019)
03/29/2019	177	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s Updated Disclosure of Invalidity Contentions filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 03/29/2019)
04/01/2019	178	ORAL ORDER: The Court, having reviewed the parties letter briefs, (D.I. 171, 172, 175, 176), relating to certain discovery disputes, (D.I. 164), concludes that the parties have well set out the issues in their briefs, and that a teleconference is unnecessary. Therefore, the Court ORDERS that today's 3:00 pm teleconference is CANCELLED. The Court will resolve the issues on the papers in short order. Ordered by Judge Christopher J. Burke on 4/1/2019. (dlb) (Entered: 04/01/2019)
04/01/2019	179	

		ORAL ORDER: The Court, having reviewed the parties' discovery dispute motion, (D.I. 164), and the parties' letter briefs relating thereto, (D.I. 171, 172, 175, 176), hereby ORDERS as follows with respect to the parties' disputes: (1) Plaintiff shall serve final infringement contentions by no later than April 15, 2019 absent further order of the Court, which shall include, at minimum, citations to source code (where applicable), (see D.I. 171 at 1-2); (2) Defendant shall make Dr. Samuel Angiuoli available for deposition by no later than April 22, 2019 absent further order of the Court; (3) Plaintiff may serve supplemental final infringement contentions (limited only to including material relating to Dr. Angiuoli's deposition), if necessary, by no later than April 29, 2019 absent further order of the Court; and (4) Defendant shall serve final noninfringement contentions and final invalidity contentions by no later than May 13, 2019 absent further order of the Court. Defendant's final noninfringement contentions shall include, at minimum, citations to source code (where applicable). Ordered by Judge Christopher J. Burke on 4/1/2019. (dlb) (Entered: 04/01/2019)
04/02/2019	180	REDACTED VERSION of 171 Letter by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 04/02/2019)
04/02/2019	181	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s [OUTSIDE ATTORNEYS' EYES ONLY] Supplemental Responses and Objections to Guardant Health, Inc.'s First Set of Interrogatories (Nos. 3-5) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 04/02/2019)
04/02/2019	182	NOTICE to Take Deposition of Daniel Simon on April 23, 2019 filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 04/02/2019)
04/02/2019	183	NOTICE to Take Deposition of Darya Chudova on April 30, 2019 filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 04/02/2019)
04/03/2019	184	REDACTED VERSION of 173 Letter, by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1)(Farnan, Brian) (Entered: 04/03/2019)
04/04/2019	185	REDACTED VERSION of 175 Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 04/04/2019)
04/05/2019	186	REDACTED VERSION of 176 Letter by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 04/05/2019)
04/05/2019	187	NOTICE to Take Deposition of Helmy Eltoukhy on April 8-9, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 04/05/2019)
04/08/2019	188	NOTICE to Take Deposition of Personal Genome Diagnostics, Inc. on 4/22/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	189	NOTICE of Subpoena to Ariosa Diagnostics, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	190	NOTICE of Subpoena to Roche Diagnostics Corporation by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	191	

		NOTICE of Subpoena to Roche Diagnostics Operations, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	192	NOTICE of Subpoena to Roche Holdings, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	193	NOTICE of Subpoena to Roche Molecular Systems, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/08/2019	194	NOTICE of Subpoena to Roche Sequencing Solutions, Inc. by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/08/2019)
04/09/2019		Pro Hac Vice Attorneys Baraa Kahf and Ioanna S. Bouris for Personal Genome Diagnostics, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d)., Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (ddp) (Entered: 04/09/2019)
04/11/2019	195	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s Objections to Guardant Health, Inc.'s Second Notice of Deposition Pursuant to Fed. R. Civ. P. 30(b)(6) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 04/11/2019)
04/15/2019	196	NOTICE to Take Deposition of Doug Ward on 4/17/2019 filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 04/15/2019)
04/15/2019	197	NOTICE OF SERVICE of (1) Defendant Personal Genome Diagnostics, Inc.'s Second Set of Interrogatories to Guardant Health, Inc. (3-14); (2) Defendant Personal Genome Diagnostics, Inc.'s Second Set of Requests for Production of Documents and Things to Guardant Health, Inc. (138-159); and (3) Defendant Personal Genome Diagnostics, Inc.'s First Set of Requests for Admissions (Nos. 1-35) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 04/15/2019)
04/15/2019	198	NOTICE OF SERVICE of Guardant Health, Inc.'s Second Amended Infringement Contentions filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/15/2019)
04/15/2019	199	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s Second Set of Common Interrogatories to Defendants (Nos. 9-11) and (ii) Guardant Health, Inc.'s Third Set of Interrogatories to Defendant (No. 10) filed by Guardant Health, Inc.. (Farnan, Brian) (Entered: 04/15/2019)
04/17/2019	200	NOTICE OF SERVICE of Third Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. to Guardant Health, Inc. (13-15) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 04/17/2019)
04/19/2019	201	NOTICE to Take Deposition of Victor Velculescu on April 19, 2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/19/2019)
04/19/2019	202	MOTION to File an Amended Pleading - filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Text of Proposed Order)Motions referred to Christopher J. Burke.(Phillips, John) (Entered: 04/19/2019)
04/19/2019	203	

		[SEALED] Letter to the Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Letter in Support of Motion for Leave to File an Amended Pleading - re 202 MOTION to File an Amended Pleading . (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Phillips, John) (Entered: 04/19/2019)
04/22/2019	204	NOTICE to Take Deposition of Personal Genome Diagnostics, Inc. on 5/1/2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/22/2019)
04/22/2019	205	NOTICE of Subpoena to Brown Rudnick LLP by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/22/2019)
04/22/2019	206	NOTICE of Subpoena to Choate, Hall & Stewart LLP by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/22/2019)
04/22/2019	207	NOTICE of Subpoena to Knobbe Martens Olson & Bear, LLP by Guardant Health, Inc. (Farnan, Brian) (Entered: 04/22/2019)
04/25/2019	208	NOTICE to Take Deposition of Amirali Talasaz (Amended) on April 30, 2019 and May 1, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 04/25/2019)
04/26/2019	209	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding No Current Amendment to Complaint. (Farnan, Brian) (Entered: 04/26/2019)
04/26/2019	210	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendant's Motion to Amend - re 202 MOTION to File an Amended Pleading . (Farnan, Brian) (Entered: 04/26/2019)
04/26/2019	211	REDACTED VERSION of 203 Letter, by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Phillips, John) (Entered: 04/26/2019)
04/29/2019	212	NOTICE OF SERVICE of (1) Defendant Personal Genome Diagnostics, Inc.s [OUTSIDE ATTORNEYS EYES ONLY] Responses and Objections to Guardant Health, Inc.s Second Set of Interrogatories (Nos. 6-9); (2) Defendant Personal Genome Diagnostics, Inc.s [OUTSIDE ATTORNEYS EYES ONLY] Responses and Objections to Guardant Health, Inc.s First Set of Common Interrogatories (Nos. 1-8); (3) Defendant Personal Genome Diagnostics, Inc.s Responses and Objections to Guardant Health, Inc.s Third Set of Requests for Production (Nos. 84-89); (4) Defendant Personal Genome Diagnostics, Inc.s Objections to Guardant Health, Inc.s Third Notice of Deposition Pursuant to Fed. R. Civ. P. 30(b)(6); (5) Defendant Personal Genome Diagnostics, Inc.s Responses and Objections to Guardant Health, Inc.s First Set of Requests for Admission (Nos. 1-21); and (6) Objections to Guardant Health, Inc.s Subpoena Duces Tecum to Knobbe, Martens, Olson & Bear, LLP filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 04/29/2019)
04/29/2019	213	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Reply Letter in Support of Motion to Amend - re 202 MOTION to File an Amended Pleading , 210 Letter. (Bilson, David) (Entered: 04/29/2019)
04/29/2019	214	

		Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding requesting teleconference - re 202 MOTION to File an Amended Pleading . (Bilson, David) (Entered: 04/29/2019)
04/30/2019	215	NOTICE OF SERVICE of Third Amended Infringement Charts filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 04/30/2019)
04/30/2019	216	ORAL ORDER: The Court, having reviewed Defendant's unopposed Motion for leave to file an Amended Answer to Second Amended Complaint, Affirmative Defenses and Counterclaims, (D.I. 202), and the parties' related letters, (D.I. 203, 210, 213, 214), HEREBY ORDERS AS FOLLOWS: (1) Defendant's unopposed Motion is GRANTED.; (2) Plaintiff's unopposed request for a 30-day extension to respond to the Amended Answer to Second Amended Complaint, Affirmative Defenses and Counterclaims is GRANTED.; (3) In light of these rulings, the parties' request for a teleconference to address Defendant's Motion is DENIED as moot.; (4) If Plaintiff wishes to file a motion to amend its complaint, it may do so, and the Court will consider such motion after it has been fully briefed. Ordered by Judge Christopher J. Burke on 4/30/2019. (dlb) (Entered: 04/30/2019)
04/30/2019	217	[SEALED] Amended ANSWER to Complaint with Jury Demand *to Second Amended Complaint, Affirmative Defenses*, COUNTERCLAIM against Guardant Health, Inc. by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 04/30/2019)
05/02/2019	218	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Discovery Teleconference. (Farnan, Brian) (Entered: 05/02/2019)
05/03/2019	219	ORAL ORDER: The Court has reviewed the parties' May 2, 2019 letter requesting a discovery teleconference regarding 3 discovery disputes. (D.I. 218) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 25), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is scheduled for May 20, 2019 at 4:00 p.m.; (3) By no later than May 8, 2019, the party seeking relief shall file with the Court a letter, not to exceed four (4) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than May 13, 2019, any party opposing the application for relief may file a letter, not to exceed four (4) pages, in no less than 12-point font, outlining that party (s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the disputes prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 5/3/2019. (dlb) Modified on 5/3/2019 (dlb). (Entered: 05/03/2019)
05/03/2019	220	NOTICE OF SERVICE of Subpoena Duces Tecum and Ad Testicandum filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Attachment)(Phillips, John) (Entered: 05/03/2019)
05/03/2019	221	

		REDACTED VERSION of 209 Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 05/03/2019)
05/03/2019	222	REDACTED VERSION of 210 Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 05/03/2019)
05/06/2019	223	SUBPOENA Returned Executed as to Illumina, Inc. on May 3, 2019 (Bilson, David) (Entered: 05/06/2019)
05/07/2019	224	MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 05/07/2019)
05/07/2019	225	MOTION to Amend/Correct 20 Amended Complaint, - filed by Guardant Health, Inc.. (Attachments: # 1 Text of Proposed Order)Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 05/07/2019)
05/07/2019	226	[SEALED] Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Opening Letter Brief in Support of Motion to File Amended Complaint - re 225 MOTION to Amend/Correct 20 Amended Complaint, . (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E)(Farnan, Michael) (Entered: 05/07/2019)
05/07/2019	227	REDACTED VERSION of 217 Answer to Complaint, Counterclaim by Personal Genome Diagnostics, Inc.. (Phillips, John) (Main Document 227 replaced on 5/7/2019) (ntl). (Entered: 05/07/2019)
05/07/2019		CORRECTING ENTRY: Corrected document added to D.I. 227 per request of counsel. (ntl) (Entered: 05/07/2019)
05/08/2019	228	NOTICE to Take Deposition of Jeffrey J. Seidel on June 13, 2019 filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 05/08/2019)
05/08/2019	229	NOTICE to Take Deposition of Vern Norviel on June 18, 2019 filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 05/08/2019)
05/08/2019	230	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding production of documents withheld as privileged. (Attachments: # 1 Exhibit 1-8)(Phillips, John) (Entered: 05/08/2019)
05/08/2019	231	[SEALED] Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7) (Farnan, Michael) (Entered: 05/08/2019)
05/13/2019	232	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Discovery Teleconference. (Farnan, Brian) (Entered: 05/13/2019)
05/13/2019	233	[SEALED] MOTION for Expedited Consideration of Discovery Dispute re 232 Letter - filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8)Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 05/13/2019)
05/13/2019	234	

		NOTICE OF SERVICE of Personal Genome Diagnostics, Inc.'s Second Updated Disclosure of Invalidity Contentions filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 05/13/2019)
05/13/2019	235	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding responding to plaintiff's May 8, 2019 discovery dispute letter - re 231 Letter,. (Attachments: # 1 Exhibit 1-8)(Phillips, John) (Entered: 05/13/2019)
05/13/2019	236	NOTICE OF SERVICE of Personal Genome Diagnostics, Inc.'s [OUTSIDE ATTORNEYS' EYES ONLY] Second Supplemental Responses and Objections to Guardant Health, Inc.'s First Set of Interrogatories (No. 2) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 05/13/2019)
05/13/2019	237	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendant's May 8, 2019 Leter - re 230 Letter. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8)(Farnan, Brian) (Entered: 05/13/2019)
05/13/2019	238	[SEALED] DECLARATION re 237 Letter, *of Helmy Eltonkhy* by Guardant Health, Inc.. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H, # 9 Exhibit I)(Farnan, Brian) (Entered: 05/13/2019)
05/13/2019	239	ORAL ORDER: The Court, having reviewed the parties May 13, 2019 letter requesting a discovery teleconference regarding 2 discovery disputes, (D.I. 232), and Plaintiffs subsequent Motion for Expedited Consideration of one of those discovery disputes (i.e., Defendants designation of Dr. Velculescu and Dr. Sausens deposition transcripts as confidential (hereinafter, Issue No. 1)), (D.I. 233), hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 25), will be modified as follows with regard to Issue No. 1: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) By no later than 5:00 pm on May 14, 2019, Plaintiff shall file with the Court a letter, not to exceed two (2) pages, in no less than 12-point font, outlining the issue in dispute and its position on that issue. By no later than 5:00 pm on May 15, 2019, Defendant may file a letter, not to exceed two (2) pages, in no less than 12-point font, outlining its reasons for its opposition.; (3) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (4) If the Court requires argument regarding Issue No. 1, it will schedule a teleconference to take place this week, but will otherwise resolve Issue No. 1 on the papers.; (5) The Court will issue a separate briefing schedule with regard to the parties second discovery dispute. Ordered by Judge Christopher J. Burke on 5/13/2019. (mlc) (Entered: 05/13/2019)
05/14/2019	240	ORAL ORDER: The Court, having reviewed the parties May 13, 2019 letter requesting a discovery teleconference regarding 2 discovery disputes, (D.I. 232), and having set a briefing schedule for the first dispute in light of Plaintiffs Motion for Expedited Consideration of that dispute, (D.I. 239), hereby ORDERS that the procedures for resolving a discovery dispute set out

		in the Scheduling Order, (D.I. 25), will be modified as follows with regard to the second dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is scheduled for June 3, 2019 at 3:00 p.m.; (3) By no later than May 16, 2019, the party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than May 21, 2019, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the disputes prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 5/14/2019. (dlb) (Entered: 05/14/2019)
05/14/2019	241	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9)(Farnan, Brian) (Entered: 05/14/2019)
05/14/2019	242	REDACTED VERSION of 226 Letter, by Guardant Health, Inc.. (Attachments: # 1 Exhibits A-E)(Farnan, Michael) (Entered: 05/14/2019)
05/14/2019	243	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding response to plaintiff's motion for leave to file third amended complaint - re 226 Letter,. (Attachments: # 1 Exhibit 1 - 4)(Phillips, John) (Entered: 05/14/2019)
05/15/2019	244	MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 05/15/2019)
05/15/2019	245	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Guardant's Motion to De-Designate Confidential Information. (Phillips, John) (Entered: 05/15/2019)
05/15/2019	246	[SEALED] DECLARATION *of Michael Untiet in Support of PGDX's Opposition to Guardant's Motion to De-Designate Confidential Material* by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5)(Phillips, John) (Entered: 05/15/2019)
05/15/2019	247	NOTICE OF SERVICE of (1) Defendant Personal Genome Diagnostics, Inc.'s Responses and Objections to Guardant Health, Inc.'s Second Set of Common Interrogatories (Nos. 9-11); and (2) Defendant Personal Genome Diagnostics, Inc.'s Responses and Objections to Guardant Health, Inc.'s Third Set of Interrogatories (No. 10) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 05/15/2019)
05/15/2019	248	NOTICE OF SERVICE of (i) Guardant Health, Inc.'s First Supplemental Initial Disclosures; (ii) Plaintiff's Supplemental Responses and Objections to Joint

		Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 1, 4, 6, 7, 8, 10, 11); (iii) Guardant Health, Inc.'s First Supplemental Responses and Objections to Personal Genome Diagnostics, Inc.'s First Set of Interrogatories (No. 2); (iv) Guardant Health, Inc.'s Responses and Objections to Personal Genome Diagnostics, Inc.'s First Set of Requests for Admissions (Nos. 1-35); (v) Guardant Health, Inc.'s Responses and Objections to Personal Genome Diagnostics, Inc.'s Second Set of Requests for Production of Documents and Things (Nos. 138-159); (vi) Guardant Health, Inc.'s Responses and Objections to Personal Genome Diagnostics, Inc.'s Second Set of Interrogatories (Nos. 3 -14); and (vii) Plaintiff's Supplemental Responses and Objections to First Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 1, 7) filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 05/15/2019)
05/16/2019	249	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s Second Supplemental Responses and Objections to Guardant Health, Inc.'s First Set of Interrogatories (Nos. 3 and 5) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 05/16/2019)
05/16/2019	250	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding discovery dispute over removal of redactions to amended answer and counterclaims. (Attachments: # 1 Exhibits 1-5)(Phillips, John) (Entered: 05/16/2019)
05/16/2019	251	ORAL ORDER: The Court, having reviewed: (1) the parties' discovery dispute motion, which concerns Plaintiff's request for an order requiring Defendant to remove confidentiality designations from specific portions of the deposition transcripts of Dr. Victor Velculescu and Dr. Mark Sausen, (D.I. 244); (2) Plaintiff's Motion for Expedited Consideration of the dispute, (D.I. 233); (3) the parties' letter briefs relating to the discovery dispute, (D.I. 241, 245); and (4) the Declaration of Michael Untiet (the "Untiet Declaration"), (D.I. 246), hereby ORDERS as follows with respect to the dispute: (1) Plaintiff's Motion for Expedited Consideration is GRANTED.; (2) Plaintiff's request for an order requiring Defendant to remove confidentiality designations from the material referenced in Paragraphs 4, 5, 8, 9 and portions of Paragraph 10 (i.e., D.I. 246, ex. 2 at 155:21-156:20) of the Untiet Declaration is GRANTED. This material is, inter alia, not the type of information that Defendant would "normally not reveal to third parties," (D.I. 30 at 2(c)), in that it is the type of information that Defendant would be normally expected to reveal to, inter alia, the United States Patent and Trademark Office in defending its patent applications. (See D.I. 241 at 2); (3) Plaintiff's request for an order requiring Defendant to remove confidentiality designations from the material referenced in Paragraphs 6, 7 and portions of Paragraph 10 (i.e., D.I. 246, ex. 2 at 156:21-157:21) of the Untiet Declaration is DENIED. This material is properly deemed confidential, in that it is the type of information that relates to: (1) Defendant's "interactions with attorneys in connection with" patent prosecution, (D.I. 246 at 6); and (2) Defendant's "views on the performance of its attorneys in connection with its patent prosecution and its commentary on the quality of the attorney work product[,]" (id. at 7, 10). The Court agrees that this type of information meets the definition of "[c]onfidential [i]nformation" set out in the Protective Order,

		including because it is information that Defendant would not normally reveal to third parties. Ordered by Judge Christopher J. Burke on 5/16/2019. (dlb) (Entered: 05/16/2019)
05/16/2019	252	NOTICE OF SERVICE of Plaintiff's Responses and Objections to Third Set of Joint Interrogatories of Defendants Foundation Medicine, Inc. and Personal Genome Diagnostics, Inc. (Nos. 13-15) filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 05/16/2019)
05/16/2019	253	REDACTED VERSION of 230 Letter by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 05/16/2019)
05/16/2019	254	REDACTED VERSION of 231 Letter, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-7)(Farnan, Michael) (Entered: 05/16/2019)
05/17/2019	255	MOTION for Teleconference to Resolve Discovery Dispute - filed by Personal Genome Diagnostics, Inc.. Motions referred to Christopher J. Burke.(Bilson, David) (Entered: 05/17/2019)
05/17/2019	256	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Reply in Support of Motion to Amend Complaint - re 225 MOTION to Amend/Correct 20 Amended Complaint, . (Attachments: # 1 Exhibit A) (Farnan, Michael) (Entered: 05/17/2019)
05/17/2019	257	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Oral Argument on Motion to Amend Complaint - re 225 MOTION to Amend/Correct 20 Amended Complaint, . (Farnan, Michael) (Entered: 05/17/2019)
05/20/2019	258	ORAL ORDER: The Court, having reviewed Plaintiffs May 20, 2019 letter requesting a teleconference to address Plaintiffs Motion to File an Amended Complaint (the Motion to Amend), (D.I. 257), HEREBY ORDERS that it will hear argument on the Motion to Amend during the teleconference set for June 3, 2019 at 3:00 p.m. (during which the Court will also hear argument regarding a discovery dispute, (see D.I. 240)). Ordered by Judge Christopher J. Burke on 5/20/2019. (dlb) (Entered: 05/20/2019)
05/20/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 5/20/2019. The Court heard argument regarding the parties' discovery dispute motion, (D.I. 224), and took the matters under advisement. (Court Reporter John Donnelly (Veritext). Clerk: M. Crawford) Appearances: B. Farnan, E. Reines, D. Walter for Plaintiff; J. Phillips, S. Larson, J. Re for Defendant. (mlc) (Entered: 05/21/2019)
05/21/2019	259	REDACTED VERSION of 237 Letter, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-8)(Farnan, Brian) (Entered: 05/21/2019)
05/21/2019	260	REDACTED VERSION of 238 Declaration, by Guardant Health, Inc.. (Attachments: # 1 Exhibits A-I)(Farnan, Brian) (Entered: 05/21/2019)
05/21/2019	261	ORAL ORDER: The Court, having reviewed the parties' discovery dispute motion relating to Defendant's request that the Court order Plaintiff to produce its communications with Dr. Helmy Eltoukhy in 2012 (the "Motion"), (D.I.

		224; D.I. 230 at 1), and the parties' letter briefs relating thereto, (D.I. 230, 237), and having heard telephonic oral argument on May 20, 2019, HEREBY ORDERS as follows with respect to the dispute: (1) The Court DENIES Defendant's Motion WITHOUT PREJUDICE to renew (i.e., the resolution that Defendant ultimately requested at the end of oral argument).; (2) The Court is sympathetic to Defendant's position that statements made by Dr. Eltoukhy in his recent Declaration, (D.I. 238), regarding Dr. Eltoukhy's level of involvement with Plaintiff in 2012, are very different than the answers that Dr. Eltoukhy and Dr. AmirAli Talasaz gave on this subject during their depositions. (Compare, e.g., D.I. 238 at 3 (Dr. Eltoukhy stating in his declaration that "my relationship as a member of the Board of Directors, an advisor and one of the largest investors was that of corporate agent and fiduciary of Guardant.", with D.I. 230, ex. 1 at 197-98 (Dr. Eltoukhy testifying that he had "no official capacity" with Plaintiff in 2012 and that he was just an "advisor" and an "investor" of Guardant as of that time frame, nothing more); D.I. 230, ex. 2 at 79-81 (Dr. Talasaz testifying that in 2012, Dr. Eltoukhy was just an advisor and investor to Guardant)); (3) The Court thus believes it would be fair to allow Defendant to take targeted, additional discovery with respect to this issue. Such discovery may include (if Defendant wishes) a supplemental deposition of Dr. Eltoukhy that may last no more than 3 hours. The parties shall meet and confer to try to reach agreement regarding the scope of such discovery. (4) After this discovery is completed, Defendant may (if it wishes) thereafter renew its Motion. Ordered by Judge Christopher J. Burke on 5/21/2019. (dlb) (Entered: 05/21/2019)
05/21/2019	262	ORAL ORDER: The Court, having reviewed the parties' discovery dispute motion relating to Plaintiff's request for additional testimony in light of assertedly non-responsive answers during the deposition of Dr. Samuel Angiuoli, a Fed. R. Civ. P. 30(b)(1) and 30(b)(6) witness for Defendant (the "Motion"), (D.I. 224 ; see also D.I. 218), and the parties' letter briefs relating thereto, (D.I. 231, 235), and having heard argument on May 20, 2019, HEREBY GRANTS Plaintiff's Motion. "[I]f a deponent fails to answer a question asked under Rule 30, or provides an answer that is evasive or incomplete, then a motion to compel the deposition testimony may be filed." Oy v. Verizon Servs. Corp., Civil Action No. 12-715-CJB, 2013 WL 5675516, at *2 (D. Del. Oct. 15, 2013) (internal quotation marks and citations omitted). During Dr. Angiuoli's deposition, Plaintiff's counsel repeatedly asked about how barcodes (as distinguished from other pieces of data) are used in the error correction process, and why barcodes are used in the error correction process (as distinguished from another piece of data). (See, e.g. D.I. 231, ex. 3 at 100-10, 125, 130, 134, 145) In response, Dr. Angiuoli merely repeated the same broad answer that barcodes are "one of many pieces of data that is being counted [in the error correction process]." (See, e.g., id. at 107; D.I. 235, ex. 1 at 229 (in response to Plaintiff's counsel asking if the step of "[t]he barcoded fragments are differentiated based on the combination of their exogenous barcode and the endogenous barcode" is "performed in the software of PlasmaSELECT 64," Dr. Angiuoli responding that "in PlasmaSELECT, as I've described, yes, barcode information, data is counted and used in addition to other pieces of data as part of an overall error correction procedure")) The substance of Dr. Angiuoli's repeated answer was simply not aligned with the

		substance of the questions that Plaintiff's counsel was asking; thus, it essentially constitutes a non-response. Plaintiff may take a supplemental Rule 30(b)(6) deposition of no more than 3 hours regarding the topic of "how and why [Defendant] uses barcodes." Ordered by Judge Christopher J. Burke on 5/21/2019. (mlc) (Entered: 05/21/2019)
05/21/2019	263	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendant's May 16, 2019 Letter - re 250 Letter. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5)(Farnan, Brian) (Entered: 05/21/2019)
05/21/2019	264	REDACTED VERSION of 233 MOTION for Expedited Consideration of Discovery Dispute re 232 Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-8)(Farnan, Brian) (Entered: 05/21/2019)
05/22/2019	265	REDACTED VERSION of 243 Letter by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 05/22/2019)
05/22/2019	266	REDACTED VERSION of 235 Letter by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 05/22/2019)
05/24/2019	267	REDACTED VERSION of 250 Letter by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Exhibits 1-5)(Phillips, John) (Entered: 05/24/2019)
05/24/2019	268	NOTICE to Take Deposition of Andrew Georgiadis on 5/29/2019 filed by Guardant Health, Inc..(Farnan, Michael) (Entered: 05/24/2019)
05/24/2019	269	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Discovery Teleconference. (Farnan, Brian) (Entered: 05/24/2019)
05/29/2019	270	REDACTED VERSION of 263 Letter, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-5)(Farnan, Brian) (Entered: 05/29/2019)
05/30/2019	271	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' May 24, 2019 letters requesting discovery dispute teleconferences regarding 4 total discovery disputes. (D.I. (269 in 1:17-cv-01623-LPS-CJB), D.I. (157 in 1:17-cv-01616-LPS-CJB) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 24 in Civil Action No. 17-1616-LPS-CJB; D.I. 25 in Civil Action No. 17-1623-LPS-CJB), will be modified as follows with regard to these disputes: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference (involving all parties in both cases) is set for 6/17/2019 at 03:00 PM before Judge Christopher J. Burke. (3) By no later than June 5, 2019, any party seeking relief shall file with the Court a letter, not to exceed four (4) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than June 11, 2019, any party opposing the application for relief may file a letter, not to exceed four (4) pages, in no less than 12-point font, outlining that party (s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the disputes prior to the telephone conference and will, in that event, cancel the conference.Ordered by Judge Christopher J. Burke on

		5/30/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 05/30/2019)
05/30/2019	272	REDACTED VERSION of 241 Letter, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-9)(Farnan, Brian) (Entered: 05/30/2019)
05/30/2019	273	REDACTED VERSION of 256 Letter, by Guardant Health, Inc.. (Attachments: # 1 Exhibit A)(Farnan, Brian) (Entered: 05/30/2019)
06/03/2019	274	STIPULATION TO EXTEND TIME Regarding Expert Discovery Deadlines to Various Dates - filed by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 06/03/2019)
06/03/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - The Court held a teleconference to address the parties' discovery dispute, (D.I. 255), and Plaintiffs Motion to File an Amended Complaint, (D.I. 225). The Court heard argument regarding the matters and took the matters under advisement. The Court granted Plaintiff's request to seal the transcript from the teleconference, and ordered the parties to follow the Court's procedures regarding redactions to the transcript. (Court Reporter Ellie Corbett (Veritext). Clerk: M. Crawford)Appearances: M. Farnan, E. Reines, D. Walter for Plaintiff; D. Bilson, S. Larson, J. Re for Defendant. (mlc) (Entered: 06/03/2019)
06/04/2019		SO ORDERED D.I. 274 STIPULATION TO EXTEND TIME Regarding Expert Discovery Deadlines to Various Dates filed by Foundation Medicine, Inc. Ordered by Judge Christopher J. Burke on 6/4/2019. (dlb) (Entered: 06/04/2019)
06/04/2019	275	ORAL ORDER: The Court, having reviewed the parties' discovery dispute motion relating to Defendant's request that Plaintiff be compelled to remove its redactions to Defendant's Amended Answer to Second Amended Complaint, Affirmative Defenses and Counterclaims ("Amended Answer and Counterclaims") (the "Motion"), (D.I. 255), and the parties' letter briefs relating thereto, (D.I. 250; D.I. 263), and having heard argument on June 3, 2019, HEREBY GRANTS Defendant's Motion for the following reasons: (1) The redactions at issue, (D.I. 263, ex. 5), are clearly related to Defendant's inequitable conduct and antitrust counterclaims. The content that Plaintiff seeks to redact relates to the alleged conduct of Plaintiff's founder while employed by another company, and Defendant cogently explains why such conduct, inter alia, is evidence of Plaintiff's inequitable conduct and demonstrates the motive behind the inequitable conduct. (See, e.g., D.I. 250, ex. 2 at 19-29); (2) "[T] here is a strong presumption in favor of public access to all judicial records and documents, including transcripts, evidence, pleadings, and other materials submitted by litigants." Mosaid Techs. Inc. v. LSI Corp., 878 F. Supp. 2d 503, 507 (D. Del. 2012) (internal quotation marks and citation omitted). Federal Rule of Civil Procedure 26(c) does permit a party to seek an order to prevent the disclosure of, inter alia, "embarrass[ing]" information contained in (for example) a pleading. Fed. R. Civ. P. 26(c). However, the party seeking such an order must "show good cause by demonstrating a particular need for protection [,]" and "[b]road allegations of harm, unsubstantiated by specific examples or articulated reasoning, do not satisfy the Rule 26(c) test." Cipollone v. Liggett

		Grp., Inc., 785 F.2d 1108, 1121 (3d Cir. 1986). "[A]n applicant... whose chief concern is embarrassment must demonstrate that the embarrassment will be particularly serious.... to succeed, a business will have to show with some specificity that the embarrassment resulting from dissemination of the information would cause a significant harm to its competitive and financial position." Id. Plaintiff has not even attempted to make such a showing. It has not provided any affidavits establishing that such embarrassment will result from disclosure of the currently-redacted allegations at issue, nor has it put forward any concrete examples in support of such a claim. See Medicines Co. v. Teva Parenteral Meds., Inc., C.A. No. 09-750-ER, 2011 WL 3290291, at *9-10 (D. Del. June 30, 2011) (finding that plaintiff failed to meet its burden of demonstrating that it would suffer particularly serious embarrassment if the disputed redactions in a pleading were disclosed to the public, where its "conclusory arguments" were "not supported by affidavit or concrete examples").; (3) Lastly, while Plaintiff suggested that the Court should wait to rule on this issue until after it has resolved Plaintiff's intended forthcoming motion to strike, filed pursuant to Federal Rule of Civil Procedure 12(f), the Court sees no reason to do so. It so concludes both because: (a) the claims and defenses in a federal civil case are generally made public in a timely fashion; and (b) the standard to prevail on such a motion to strike will be even more difficult for Plaintiff to meet than the standard at issue here, see The Penn Mut. Life Ins. Co. v. Norma Espinosa 2007-1 Ins. Trust, C.A. No. 09-300-LPS, 2011 WL 710970, at *4 (D. Del. Feb. 22, 2011) (explaining that even if the challenged material is scandalous, a Rule 12(f) "motion to strike should not be granted, unless the allegations have no possible relation to the controversy and will prejudice the adverse party"). Ordered by Judge Christopher J. Burke on 6/4/2019. (mlc) (Entered: 06/04/2019)
06/05/2019	276	AMENDED DOCUMENT by Personal Genome Diagnostics, Inc.. Amendment to 227 Redacted Document *Amended version of redacted Amended Answer to Second Amended Complaint and Counterclaims (amended pursuant to the Court's June 4, 2019 oral order (D.I. 275)).* (Phillips, John) (Entered: 06/05/2019)
06/05/2019	277	ORAL ORDER: The Court, having considered Plaintiff's "Motion to File A[] [Third] Amended Complaint" (the "Motion"), (D.I. 225), and the parties' letter briefs relating thereto, (D.I. 226; D.I. 243; D.I. 256), and having heard argument on June 3, 2019, HEREBY GRANTS Plaintiff's Motion for the following reasons: (1) Defendant primarily argues that Plaintiff's motion should be denied because its proposed Third Amended Complaint is futile, in that it fails to sufficiently plead willful infringement. (D.I. 243 at 2-3) "[I]n assessing futility of a proposed amendment, the same standard of legal sufficiency as under Rule 12(b)(6) is applied." Cornell Univ. v. Illumina, Inc., C.A. No. 10-433-LPS-MPT, 2017 WL 89165, at *3 (D. Del. Jan. 10, 2017) (internal quotation marks and citation omitted). "[I]n order to sufficiently plead willful infringement, a plaintiff must allege facts plausibly showing that as of the time of the claim's filing, the accused infringer: (1) knew of the patent-in-suit; (2) after acquiring that knowledge, it infringed the patent; and (3) in doing so, it knew, or should have known, that its conduct amounted to infringement of the patent." Valinge Innovation AB v. Halstead New England Corp., Civil

		Action No. 16-1082-LPS-CJB, 2018 WL 2411218, at *13 (D. Del. May 29, 2018). Plaintiff's willful infringement allegations are not futile because they plausibly allege that: (a) Defendant knew of the '731 patent and Plaintiff's three other relevant patent applications as of July 2017 (and, relatedly, knew of those three other patents as of the dates they issued); and (b) Defendant falsely claimed that it did not learn of all four of patents-in-suit until the date of Plaintiff's respective complaints -- a claim that was "designed to conceal [Defendant's] willful infringement." (D.I. 226, ex. B at 11-14) These pleaded facts, plus certain other alleged facts suggesting that Defendant was thereafter willfully infringing valid patents, are enough to meet Plaintiff's burden.; (2) Plaintiff's Motion comes after the deadline for amendments to pleadings set out in the Scheduling Order, (D.I. 25), and Plaintiff must therefore show good cause to modify the schedule. Fed. R. Civ. P. 16(b)(4); Meda Pharms. Inc. v. Teva Pharms. USA, Inc., C.A. No. 15-785-LPS, 2016 WL 6693113, at *1 (D. Del. Nov. 14, 2016). Plaintiff has demonstrated good cause here, where its newly-proposed willful infringement allegations are largely based on deposition testimony from Dr. Velculescu, a founder of Defendant, that was given on April 19, 2019, several months after the deadline for amendments to pleadings. (D.I. 226 at 1-2; D.I. 256 at 1-2); (3) Lastly, with respect to Defendant's argument that Plaintiff's proposed amended pleading "is futile and prejudicial" to Defendant because it breaches the parties' agreement that Guardant "will not argue to a jury that the fact that [Defendant withdrew] its petitions for [post-grant review of certain asserted patents] is evidence that the challenged patents are valid" or that Defendant "acted improperly by filing or withdrawing the petitions[,]" (D.I. 243 at 1 (emphasis omitted)), the Court makes no ruling on what the jury can or cannot be told with respect to the agreement at this time. The Court would find that Plaintiff's willfulness allegations are not futile, even setting aside the allegations relating to Defendant's withdrawal of its petitions for post-grant review. If necessary, the Court can take up the issue later in the case when it has a more fully developed record on the issue. Ordered by Judge Christopher J. Burke on 6/5/2019. (mlc) (Entered: 06/05/2019)
06/05/2019	278	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6)(Farnan, Michael) (Entered: 06/05/2019)
06/06/2019	279	NOTICE of Intent to Request Redaction of Transcript of certain portions of the transcript of May 20, 2019 teleconference with Judge Burke by Personal Genome Diagnostics, Inc. re Discovery Conference, (Bilson, David) (Entered: 06/06/2019)
06/10/2019	280	[SEALED] Third AMENDED COMPLAINT against Personal Genome Diagnostics, Inc.- filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 5, # 6 Exhibit 6, # 7 Exhibit 7, # 8 Exhibit 8, # 9 Exhibit 9, # 10 Exhibit 10, # 11 Exhibit 11, # 12 Exhibit 12)(Farnan, Michael) (Entered: 06/10/2019)
06/11/2019	281	

		Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding IPR Proceeding. (Attachments: # 1 Exhibit A)(Farnan, Brian) (Entered: 06/11/2019)
06/11/2019	282	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding in response to Plaintiff's June 5, 2019 discovery dispute letter - re 278 Letter. (Attachments: # 1 Exhibit 1)(Phillips, John) (Entered: 06/11/2019)
06/11/2019	283	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding response to Plaintiff's June 11, 2019 letter re IPR proceeding - re 281 Letter. (Phillips, John) (Entered: 06/11/2019)
06/13/2019	284	[SEALED] ANSWER to Amended Complaint, re: 280 Amended Complaint, with Jury Demand *Affirmative Defenses and*, COUNTERCLAIM against Guardant Health, Inc. by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 06/13/2019)
06/13/2019	285	[SEALED] MOTION to Dismiss for Failure to State a Claim - filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2)Motions referred to Christopher J. Burke.(Farnan, Michael) (Entered: 06/13/2019)
06/13/2019	286	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendant's June 11, 2019 Letter - re 283 Letter. (Attachments: # 1 Exhibit A)(Farnan, Brian) (Entered: 06/13/2019)
06/14/2019	287	ORAL ORDER: The Court hereby ORDERS that the discovery dispute teleconference scheduled for 6/17/2019 at 3:00 pm is hereby rescheduled for 6/17/2019 at 10:00 am. Ordered by Judge Christopher J. Burke on 6/14/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 06/14/2019)
06/14/2019	288	[SEALED] MOTION [Defendant Personal Genome Diagnostics, Inc.'s Unopposed Motion to Redact Transcript of discovery dispute conference held with the Court on May 20, 2019] *(Transcript does not appear on docket)* - filed by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Text of Proposed Order, # 2 Exhibit A, # 3 Exhibit B)Motions referred to Christopher J. Burke. (Bilson, David) (Entered: 06/14/2019)
06/17/2019	289	Official Transcript of Telephone Conference held on June 3, 2019 before Judge Christopher J. Burke. Court Reporter Veritext Reporting Service, Telephone number (302) 571-0510. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 7/8/2019. Redacted Transcript Deadline set for 7/18/2019. Release of Transcript Restriction set for 9/16/2019. (bpg) (Entered: 06/17/2019)
06/17/2019	290	Official Transcript of Case Management Conference held on May 20, 2019 before Judge Christopher J. Burke. Court Reporter John Donnelly of Veritext Legal Solutions, Telephone number (302) 571-0510. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 7/8/2019. Redacted

		Transcript Deadline set for 7/18/2019. Release of Transcript Restriction set for 9/16/2019. (bpg) (Entered: 06/17/2019)
06/17/2019	291	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Guardant's June 13, 2019 letter - re 286 Letter. (Phillips, John) (Entered: 06/17/2019)
06/17/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 6/17/2019. The Court heard argument. The Court considers Defendant Foundation Medicine Inc.'s dispute to be moot. The Court denied Plaintiff's motion without prejudice to renew if the estoppel issue becomes relevant. The transcript will serve as the Court's order. (Court Reporter Carrie Gold (Veritext). Clerk: M. Crawford) Appearances: B. Farnan, E. Reines, J. Constant for Plaintiff; J. Tigan, K. Jacobs, E. Marandett, M. Ives, M. Barrett, E. Miller for Defendant Foundation Medicine, Inc.; J. Phillips, S. Larson, J. Re for Defendant Personal Genome Diagnostics, Inc. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 06/17/2019)
06/19/2019	292	Joint MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 06/19/2019)
06/19/2019	293	ORDER granting D.I. 288 MOTION [Defendant Personal Genome Diagnostics, Inc.'s Unopposed Motion to Redact Transcript of discovery dispute conference held with the Court on May 20, 2019]. Signed by Judge Christopher J. Burke on 6/19/2019. (mlc) (Entered: 06/19/2019)
06/19/2019	294	REDACTED VERSION of 280 Amended Complaint, by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-12)(Farnan, Michael) (Entered: 06/19/2019)
06/20/2019	295	Redacted version of 290 Transcript (dlb) (Entered: 06/20/2019)
06/20/2019	296	REDACTED VERSION of 284 Answer to Amended Complaint, Counterclaim by Personal Genome Diagnostics, Inc.. (Bilson, David) (Entered: 06/20/2019)
06/21/2019	297	REDACTED VERSION of 288 MOTION [Defendant Personal Genome Diagnostics, Inc.'s Unopposed Motion to Redact Transcript of discovery dispute conference held with the Court on May 20, 2019] *(Transcript does not appear on docket)* by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Text of Proposed Order, # 2 Exhibit A, # 3 Exhibit B)(Bilson, David) (Entered: 06/21/2019)
06/24/2019	298	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Discovery Conference. (Farnan, Brian) (Entered: 06/24/2019)
06/24/2019	299	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Addressing Dispute Over Antitrust Claim. (Farnan, Brian) (Entered: 06/24/2019)
06/24/2019	300	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' June 24, 2019 letter requesting a discovery dispute teleconference regarding 1 discovery dispute. (D.I. 298) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 25), will be

		modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is set for 7/2/2019 at 03:00 PM before Judge Christopher J. Burke. (3) By no later than June 26, 2019, any party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than June 28, 2019, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 6/24/2019. (dlb) (Entered: 06/24/2019)
06/24/2019	301	ORAL ORDER: The Court, having reviewed the parties' June 24, 2019 letter requesting a briefing process to address the parties' dispute over whether discovery on Defendant's antitrust claims should be postponed, (D.I. 299), HEREBY ORDERS that Plaintiff shall file an opening letter brief of no more than 5 pages to be followed, seven days later, by Defendant's responsive letter of no more than five pages. Ordered by Judge Christopher J. Burke on 6/24/2019. (mlc) (Entered: 06/24/2019)
06/25/2019	302	Official Transcript of Telephone Conference held on June 17, 2019 before Judge Christopher J. Burke. Court Reporter Services by Veritext Legal Solutions, Telephone (302) 571-0150. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 7/16/2019. Redacted Transcript Deadline set for 7/26/2019. Release of Transcript Restriction set for 9/23/2019. (bpg) (Entered: 06/25/2019)
06/26/2019	303	Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Request for Discovery Teleconference. (Tigan, Jeremy) (Entered: 06/26/2019)
06/26/2019	304	Letter to Judge Burke from Brian Farnan regarding Bifurcation. (Farnan, Brian) (Additional attachment(s) added on 6/27/2019: # 1 Exhibit 1) (dlb). (Entered: 06/26/2019)
06/26/2019	305	[SEALED] Letter re: Discovery Dispute to Judge Burke from Brian Farnan. (Attachments: # 1 Exhibit, # 2 Exhibit)(Farnan, Brian) Modified on 6/27/2019 (dlb). (Entered: 06/26/2019)
06/27/2019	306	STIPULATION regarding Plaintiff's Answer to Defendant's Counterclaims re 284 Answer to Amended Complaint, Counterclaim by Guardant Health, Inc.. (Farnan, Brian) (Entered: 06/27/2019)
06/27/2019		SO ORDERED D.I. 306 Stipulation that Plaintiffs previously filed Motion to Dismiss (D.I. 285) Count XII of Defendants counterclaims for unenforceability based on inequitable conduct with respect to the 992 Patent shall serve as Plaintiffs response to Defendants Counterclaims set forth in its June 13, 2019

		Answer to Third Amended Complaint, Affirmative Defenses And Counterclaims (D.I. 284). Ordered by Judge Christopher J. Burke on 6/27/2019. (dlb) (Entered: 06/27/2019)
06/27/2019	307	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' June 26, 2019 letter requesting a discovery dispute teleconference regarding 1 discovery dispute. (D.I. 303 in 1:17-cv-01623-LPS-CJB; D.I. 171 in 17-cv-01616-LPS-CJB) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 24 in Civil Action No. 17-1616-LPS-CJB; D.I. 25 in Civil Action No. 17-1623-LPS-CJB), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is set for 7/22/2019 at 4:00 PM before Judge Christopher J. Burke. (3) By no later than July 8, 2019, any party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than July 15, 2019, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 6/27/2019. Associated Cases: 1:17-cv-01623-LPS-CJB, 1:17-cv-01616-LPS-CJB(dlb) (Entered: 06/27/2019)
06/27/2019	308	[SEALED] ANSWERING BRIEF in Opposition re 285 MOTION to Dismiss for Failure to State a Claim filed by Personal Genome Diagnostics, Inc..Reply Brief due date per Local Rules is 7/5/2019. (Attachments: # 1 Exhibits 1-4) (Phillips, John) (Entered: 06/27/2019)
06/28/2019	309	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Letter in Opposition to Guardant's Motion to Compel Production of Privileged Notes and Communications. (Attachments: # 1 Exhibit 1)(Phillips, John) (Entered: 06/28/2019)
06/28/2019	310	[SEALED] DECLARATION re 309 Letter, *of Sam Angiuoli In Support of PGDX's Opposition to Guardant's Motion to Compel* by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 06/28/2019)
07/01/2019	311	MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 07/01/2019)
07/02/2019	312	ORAL ORDER: The Court, having reviewed the parties' discovery dispute motion relating to Plaintiff's request that the Court order Defendant to produce drafts and communications relating to notes that Dr. Samuel Angiuoli used during his court-ordered supplemental 30(b)(6) deposition (the "Motion"), (D.I. 311), and the parties' letter briefs relating thereto, (D.I. 305, 309), HEREBY DENIES Plaintiff's Motion, and in so doing, states as follows: (1) Plaintiff argues that Defendant waived attorney client privilege and work product protection over prior drafts and correspondence related to Dr. Angiuoli's notes

		by producing the notes to Plaintiff during the deposition. (D.I. 305 at 2-3) It is Plaintiff's burden to demonstrate that a waiver has occurred. See, e.g., Rockwell Automation, Inc. v. Radwell Int'l, Inc., Civil No. 15-5246(RBK/JS), 2019 WL 1864198, at *3 (D.N.J. Apr. 25, 2019) ("The party alleging that a waiver [of work product] occurred has the burden of proof on the waiver issue."); New Jersey Mfrs. Ins. Co. v. Brady, CIVIL ACTION NO. 3:15-CV-02236, 2017 WL 264457, at *8 (M.D. Pa. Jan. 20, 2017) (noting that in the circumstance at play here, "the party challenging the privilege bears the burden of demonstrating that a waiver of the attorney-client privilege has occurred").; (2) Plaintiff's Motion is premised on the view that Dr. Angiuoli's notes constitute a "written script prepared by counsel[.]" (D.I. 305 at 2) However, the record does not bear this out. Dr. Angiuoli submitted a Declaration in which he explains that: (a) he prepared notes (which were about a page and a half long) in advance of his supplemental deposition in consultation with Defendant's attorney to ensure that his testimony would satisfy Defendant's obligations under the Court's order requiring the supplemental deposition; (b) he never relied on his notes or drafts thereof to refresh his recollection; (c) he read the notes on the record in response to a request from Plaintiff's attorney to refer to the relevant portion of the notes; and (d) he answered the vast majority of Plaintiff's counsel's questions without referring to the notes. (D.I. 310; see also D.I. 309 at 1-2) (3) Plaintiff asserts that the facts here are similar to those in In re Neurontin Antitrust Litig., MDL Docket No. 1479, 2011 WL 253434 (D.N.J. Jan. 25, 2011). (D.I. 305 at 2-3) In that case, the Court found that the defendants waived work product protection by handing over a 46-page outline created entirely by litigation counsel for a Rule 30(b)(6) witness, who was not permitted to testify without the outline and added nothing beyond what was in the outline. Id. at *9-10, *17. As described above, the record here is much different from the facts of Neurontin. (D.I. 309 at 2-3); (4) Plaintiff also suggests that the drafts and communications relating to Dr. Angiuoli's notes should be turned over under the three-part test set out in Sporck v. Peil, 759 F.2d 312 (3d Cir. 1985) for obtaining documents used by a witness prior to testifying. (D.I. 305 at 2 & n.6) Under that test: (a) the witness must use the writing to refresh his memory; (b) the witnesses must use the writing for the purpose of testifying; and (c) the court must determine that production is necessary in the interests of justice. Sporck, 759 F.2d at 317. However, Dr. Angiuoli did not rely on his notes (nor any drafts or communications relating to the notes) to refresh his recollection. (D.I. 309 at 3; D.I. 310 at 3); (5) While the caselaw suggests that generally, if a witness brings a document to a deposition and reads or refers to part of it, the witness must turn over only the parts that he or she reads or refers to, (see, e.g., S & A Painting Co. v. O.W.B. Corp., 103 F.R.D. 407, 409 (W.D. 1984); D.I. 309 at 2), Plaintiff has not pointed the Court to any case where a court permitted a party to take discovery regarding prior drafts of such notes or the witness's communications with his attorneys in order to prepare the notes under the circumstances at play here. (6) Today's 3:00 p.m. teleconference is CANCELLED. Ordered by Judge Christopher J. Burke on 7/2/2019. (mlc) (Entered: 07/02/2019)
07/02/2019	313	Joint MOTION for Teleconference to Resolve Discovery Dispute - filed by Foundation Medicine, Inc.. Motions referred to Christopher J. Burke.(Tigan, Jeremy) (Entered: 07/02/2019)

07/03/2019	314	Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding PGD's Opposition to Plaintiff's Motion to Bifurcate - re 304 Letter. (Phillips, John) (Entered: 07/03/2019)
07/05/2019	315	REPLY BRIEF re 285 MOTION to Dismiss for Failure to State a Claim filed by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2)(Farnan, Brian) (Entered: 07/05/2019)
07/05/2019	316	REDACTED VERSION of 309 Letter, *and Exhibit 1 Thereto* by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Exhibit 1)(Bilson, David) (Entered: 07/05/2019)
07/05/2019	317	REDACTED VERSION of 310 Declaration by Personal Genome Diagnostics, Inc.. (Bilson, David) (Entered: 07/05/2019)
07/05/2019	318	REDACTED VERSION of 308 Answering Brief in Opposition, *and Exhibits 1 - 4* by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Exhibit 1 - 4) (Bilson, David) (Entered: 07/05/2019)
07/08/2019	319	NOTICE to Take Deposition of Gangwu Mei on July 11, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 07/08/2019)
07/08/2019	320	REDACTED VERSION of 285 MOTION to Dismiss for Failure to State a Claim by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-2)(Farnan, Brian) (Entered: 07/08/2019)
07/08/2019	321	REDACTED VERSION of 286 Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibit A)(Farnan, Brian) (Entered: 07/08/2019)
07/08/2019	322	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Oral Argument - re 304 Letter. (Farnan, Brian) (Entered: 07/08/2019)
07/08/2019	323	[SEALED] Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Discovery Disputes. (Attachments: # 1 Exhibit 1-9)(Tigan, Jeremy) (Entered: 07/08/2019)
07/15/2019	324	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendants' July 8, 2019 Letter - re (178 in 1:17-cv-01616-LPS-CJB, 323 in 1:17-cv-01623-LPS-CJB) Letter. (Farnan, Brian) (Entered: 07/15/2019)
07/16/2019	325	REDACTED VERSION of 323 Letter by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Exhibits 1-9)(Bilson, David) (Entered: 07/16/2019)
07/16/2019	326	ORAL ORDER: The Court hereby orders as follows regarding Plaintiffs motion to stay and bifurcate Defendants antitrust counterclaims (the motion): (1) Telephonic argument shall be held on July 23, 2019 at 11:30am regarding the motion. Plaintiff shall initiate the call to 302-573-4595.; (2) For the Courts administrative purposes, Plaintiff shall file a one-page document entitled Motion to Stay and Bifurcate Defendants Antitrust Counterclaims by July 18, 2019. Ordered by Judge Christopher J. Burke on 7/16/2019. (dlb) (Entered: 07/16/2019)

07/16/2019	327	MOTION to Stay *and Bifurcate Defendant's Antitrust Counterclaims* - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 07/16/2019)
07/17/2019	328	REDACTED VERSION of 305 Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-2)(Farnan, Brian) (Entered: 07/17/2019)
07/17/2019	329	NOTICE OF SERVICE of Defendant Personal Genome Diagnostics, Inc.'s [CONFIDENTIAL - OUTSIDE ATTORNEYS' EYES ONLY] Third Supplemental Responses and Objections to Guardant Health, Inc.'s First Set of Interrogatories (No. 5) filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 07/17/2019)
07/19/2019	330	MOTION permission to attend July 22, 2019 telephonic discovery conference regarding motion to compel certain Illumina Confidential documents - filed by Illumina, Inc.. Motions referred to Christopher J. Burke.(Morrison, Susan) (Entered: 07/19/2019)
07/19/2019		SO ORDERED D.I. (330 in 1:17-cv-01623-LPS-CJB, 184 in 1:17-cv-01616-LPS-CJB) MOTION permission to attend July 22, 2019 telephonic discovery conference regarding motion to compel certain Illumina Confidential documents filed by Illumina, Inc.. Ordered by Judge Christopher J. Burke on 7/19/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 07/19/2019)
07/23/2019	331	REDACTED VERSION of (324 in 1:17-cv-01623-LPS-CJB, 180 in 1:17-cv-01616-LPS-CJB) Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 07/23/2019)
07/23/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Telephonic oral argument held on 7/23/2019 regarding D.I. 327 MOTION to Stay *and Bifurcate Defendant's Antitrust Counterclaims* filed by Guardant Health, Inc. The Court will issue an order. (Court Reporter Valerie Gunning. Clerk: M. Crawford) Appearances: M. Farnan, E. Reines, D. Walter for Plaintiff; J. Phillips, W. Zimmerman, S. Larson, J. Re for Defendant Personal Genome Diagnostics, Inc.; K. Jacobs, M. Marandett, M. Ives for Foundation Medicine, Inc. (mlc) (Entered: 07/23/2019)
07/23/2019	332	ORAL ORDER:The Court, having considered Plaintiff's "Motion to Stay and Bifurcate Defendant's Antitrust Counterclaims" (the "Motion"), (D.I. 327), and the parties' letter briefs relating thereto, (D.I. 304, 314), and having heard argument on July 23, 2019, HEREBY DENIES Plaintiff's Motion for the following reasons: (1) The party moving for bifurcation bears the burden of establishing that it is appropriate. Sepracor Inc. v. Dey L.P., Civil Action No. 06-113-JJF, 2010 WL 2802611, at *3 (D. Del. July 15, 2010). The standard for bifurcation is set forth in Federal Rule of Civil Procedure 42(b), and pursuant to that rule, courts, when exercising their broad discretion as to whether to bifurcate issues for trial, should consider whether bifurcation will avoid prejudice, conserve judicial resources, and enhance juror comprehension of the issues presented in the case. Id. Furthermore, when deciding whether an issue should be bifurcated, courts must ensure that a litigant's constitutional right to a jury is preserved. Shum v. Intel Corp., 499 F.3d 1272, 1276 (Fed. Cir. 2007).;

(2) Five months ago, Plaintiff agreed to extend Defendant's deadline to amend its defenses and counterclaims relating to the Complaint to May 3, 2019. (D.I. 140) On April 19, 2019, Defendant timely moved to file its Amended Answer to Second Amended Complaint, Affirmative Defenses and Counterclaims ("Amended Answer"), which sets forth, inter alia, Walker Process antitrust counterclaims. (D.I. 203 at 1) In that motion, Defendant explained that grant of its motion would not cause undue prejudice to Plaintiff because, inter alia: (a) the antitrust counterclaims would require little additional discovery; (b) the parties had already engaged in considerable discovery regarding the relevant market in connection with Plaintiff's damages claims; and (c) to the extent Plaintiff required additional discovery, Defendant would agree to a reasonable extension. (D.I. 203 at 2-3) In Plaintiff's April 26, 2019 response, Plaintiff did not oppose Defendant's request to amend its pleading; moreover, although Plaintiff referenced the subject of discovery in that letter, it made no assertion therein that any discovery-related concerns would cause it undue prejudice were amendment granted. (D.I. 210 at 1) Four days later, on April 30, 2019, Defendant filed its Amended Answer. (D.I. 217) Yet now, with the instant Motion, Plaintiff claims that because only 15 days were left in the discovery period when Defendant filed its Amended Answer, that was too late. (D.I. 304 at 3 (Plaintiff asserting that considerations of prejudice to it justify bifurcation and stay of Defendant's antitrust counterclaims because Defendant "raised its antitrust counterclaims with just 15 days left in the fact discovery period, leaving no time for the parties to conduct any meaningful discovery related [to] these claims")) Plaintiff's late-arriving concerns regarding the scope of discovery on Defendant's antitrust counterclaims suggests that allowing the antitrust counterclaims to proceed forward would not truly be highly prejudicial to Plaintiff.; (3) In its discovery dispute letter, one of Plaintiff's most significant arguments (indeed, its primary argument, which it repeated throughout) was that bifurcation is warranted here because Defendant's antitrust counterclaims will be moot if Defendant cannot first prove that Plaintiff committed inequitable conduct. (D.I. 304 at 1, 3, 5) Under precedent of the Supreme Court of the United States, however, when factual issues common to both legal and equitable claims are involved in a single case, the legal claims must be determined by the jury prior to any final court determination of the equitable claims. See Shum, 499 F.3d at 1277. Defendant's inequitable conduct defense is an equitable claim, while its antitrust counterclaims are legal in nature; yet these claims share common factual elements. See Schering Corp. v. Mylan Pharms. Inc., Civil Action No. 09-6383 (JLL), 2010 WL 11474547, at *1 (D.N.J. June 10, 2010). Both claims, for example, rely on allegations of misrepresentation to the United States Patent Office during patent prosecution. (D.I. 314 at 3); Schering, 2010 WL 11474547, at *1. Thus, it appears that bifurcation of Defendant's antitrust counterclaims would violate Defendant's right to a trial by jury on such claims, because it would require the Court to resolve Defendant's inequitable conduct defense prior to Defendant's antitrust counterclaims. (D.I. 314 at 1-3); Schering, 2010 WL 11474547, at *1; Celgene Corp. v. Barr Labs., Inc., Civil Action No. 07-286 (SDW), 2008 WL 2447354, at *2-3 (D.N.J. June 13, 2008).; and (4) It does not appear to be in dispute that there would be substantial overlap between Defendant's antitrust counterclaims and its defenses of

		inequitable conduct and improper inventorship. (D.I. 304 at 5; D.I. 314 at 4) There also appears to be some overlap between the monopoly power issues relevant to Defendant's antitrust counterclaims and the facts Plaintiff would need to prove regarding damages about the relevant market. In light of this, the Court is not convinced that bifurcation at this stage would promote the efficient use of judicial resources. See, e.g., Malibu Boats, LLC v. MasterCraft Boat Co., No. 3:16-CV-82-TAV-HBG, 2016 WL 8317032, at *2 (E.D. Tenn. Oct. 28, 2016) (denying motion to bifurcate and stay discovery on antitrust counterclaim where, inter alia, "because both the impending antitrust counterclaim and the patent unenforceability counterclaim will turn in large part upon the same alleged 'inequitable conduct' of Malibu employees before the USPTO, there is likely to be significant evidentiary overlap between the patent and antitrust issues" and therefore "bifurcation at this juncture would not promote judicial economy, reduce jury confusion, or conserve resources"); Procter & Gamble Co. v. CAO Grp., No. 1:13-cv-337, 2013 WL 6061103, at *3 (S.D. Ohio Nov. 18, 2013) ("While bifurcating and staying the antitrust issues would certainly reduce the requisite discovery, there is a substantial overlap between the patent [issues, i.e., an inequitable conduct affirmative defense] and antitrust claims, and overlap weighs strongly in favor of consolidated discovery and trial."); Masimo Corp. v. Mindray DS USA Inc., Case No.: SACV 12-02206-CJC(JPRx), 2013 WL 12129654, at *7 (C.D. Cal. July 17, 2013) (finding that bifurcation and a stay of discovery regarding defendant's antitrust claims was not warranted where "[t]here are significant overlapping issues between the patent and antitrust claims" and thus "[t]he determination of each will likely involve similar issues and evidence"). Ordered by Judge Christopher J. Burke on 7/23/2019. (mlc) (Entered: 07/23/2019)
07/25/2019	333	NOTICE OF SERVICE of Expert Report of Bradley N. Reiff and Opening Expert Report of Olivier Harismendy, Ph.D. filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 07/25/2019)
07/25/2019	334	NOTICE OF SERVICE of (i) Expert Report of Stephen L. Becker, Ph.D. with Regard to Personal Genome Diagnostics, Inc. and (ii) Expert Report of Gregory Cooper, Ph.D. filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 07/25/2019)
07/26/2019	335	ORAL ORDER: The Court hereby ORDERS that the discovery dispute teleconference regarding the parties' Joint Motion for a Teleconference to Resolve Discovery Dispute, (D.I. 176 in 17-1616-LPS-CJB; D.I. 313 in 17-1623-LPS-CJB), is rescheduled for 8/5/2019 at 4:00 PM before Judge Christopher J. Burke.Ordered by Judge Christopher J. Burke on 7/26/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 07/26/2019)
08/05/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 8/5/2019. The Court heard argument regarding Defendants' discovery dispute, (D.I. 176 in 17-1616-LPS-CJB; D.I. 313 in 17-1623-LPS-CJB), and took the matter under advisement. (Court Reporter Heather Triozzi. Clerk: M. Crawford) Appearances: B. Farnan, E. Reines, J. Constant for Plaintiff; K. Jacobs, E. Marandett, M. Ives for

		Defendant Foundation Medicine, Inc.; J. Phillips, B. Zimmerman, S. Larson, J. Re for Defendant Personal Genome Diagnostics, Inc.; S. Morrison, M. Amon for non-party Illumina, Inc. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 08/06/2019)
08/06/2019	336	OBJECTIONS by Guardant Health, Inc. to 332 Oral Order,,,,,,,,,,,,,,,,,,,,,,,,, . (Attachments: # 1 Certification of Compliance)(Farnan, Michael) (Entered: 08/06/2019)
08/07/2019	337	ORAL ORDER: The Court, having reviewed the parties' discovery dispute motion relating to Defendants' request that Plaintiff be compelled to produce documents related to Dr. Eltoukhy's employment at Illumina, Inc. ("Illumina") and involvement with Guardant in the 2012 time period (the "Motion"), (D.I. 176 in Civil Action No. 17-1616-LPS-CJB; D.I. 313 in Civil Action No. 17-1623-LPS-CJB), and the parties' letter briefs relating thereto, (D.I. 178; D.I. 180 in Civil Action No. 17-1616-LPS-CJB; D.I. 323; D.I. 324 in Civil Action No. 17-1623-LPS-CJB), and having heard argument on August 5, 2019, hereby ORDERS as follows with respect to Defendants' Motion: (1) Plaintiff has returned to Illumina approximately 51,000 documents that could contain relevant information. By no later than August 14, 2019, Defendants shall: (a) meet and confer with Illumina to see if they can agree to a process for determining search terms and subsequent production of relevant, non-privileged documents from this category of documents; and (b) submit a joint status report (along with Plaintiff) indicating whether Defendant and Illumina have reached agreement on such a process, and if they have not, indicating the issues that remain in dispute and the parties and Illuminas respective positions. (2) There are approximately 4,000-5,000 additional documents in Plaintiff's control that have not been produced but that could contain relevant information. By no later than August 13, 2019, Defendants shall provide Plaintiff with a list of reasonable search terms. By no later than August 19, 2019, Plaintiff shall indicate whether it has any objections thereto. If there are no disputes, Plaintiff shall search the documents in this category utilizing the agreed-upon search terms and shall produce relevant, non-privileged documents promptly thereafter. If there are disputes regarding the search terms, the parties shall further meet and confer to attempt to resolve them. If the parties cannot resolve any further disputes relating to these documents, they shall utilize the Courts discovery dispute procedures. (3) Defendants' Motion is DENIED-AS-MOOT in light of the agreements reached among the parties and Illumina with respect to the documents at issue as described above. Ordered by Judge Christopher J. Burke on 8/7/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 08/07/2019)
08/12/2019	338	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Request for Discovery Teleconference. (Farnan, Michael) (Entered: 08/12/2019)
08/13/2019	339	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' August 12, 2019 letter requesting a discovery dispute teleconference regarding one discovery dispute. (D.I. 338). It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 25), will be modified as follows with regard to this dispute: (1) The parties shall file a joint

		"Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is set for September 4, 2019 at 1:00 PM before Judge Christopher J. Burke. (3) By no later than August 21, 2019, any party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than August 28, 2019, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference. Ordered by Judge Christopher J. Burke on 8/13/2019. (dlb) (Entered: 08/13/2019)
08/13/2019	340	MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 08/13/2019)
08/15/2019	341	Joint STATUS REPORT by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 08/15/2019)
08/20/2019	342	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding September 4, 2019 Hearing - re 339 Order Setting Teleconference,,,,,. (Farnan, Brian) (Entered: 08/20/2019)
08/20/2019	343	RESPONSE TO OBJECTIONS by Personal Genome Diagnostics, Inc. re 336 Objections *Defendant's Response to Plaintiff's Objections to Magistrate Judge's July 23, 2019 Order (D.I. 332).* (Attachments: # 1 Exhibit 1)(Bilson, David) (Entered: 08/20/2019)
08/21/2019	344	ORAL ORDER: The Court, having reviewed the parties August 20, 2019 letter, (D.I. 342), hereby ORDERS that the discovery dispute teleconference set for September 4, 2019 at 1:00pm is CANCELED. Ordered by Judge Christopher J. Burke on 8/21/2019. (dlb) (Entered: 08/21/2019)
08/22/2019	345	[SEALED] NOTICE of Subsequent Activity Concerning Guardant's Motion to Dismiss (D.I. 285) by Guardant Health, Inc. (Attachments: # 1 Exhibit 1) (Farnan, Michael) (Entered: 08/22/2019)
08/23/2019	346	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding response to Plaintiff's Notice of Subsequent Activity - re 345 Notice (Other). (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Phillips, John) (Main Document 346 replaced on 8/23/2019) (dlb). (Entered: 08/23/2019)
08/29/2019	347	Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Request for Discovery Teleconference. (Farnan, Brian) (Entered: 08/29/2019)
08/29/2019	348	ORAL ORDER Setting Teleconference: The Court has reviewed the parties' August 29, 2019 letter requesting a discovery dispute teleconference regarding 1 discovery dispute. (D.I. (347 in 1:17-cv-01623-LPS-CJB, 201 in 1:17-cv-01616-LPS-CJB) It hereby ORDERS that the procedures for resolving a discovery dispute set out in the Scheduling Order, (D.I. 24 in Civil Action No.

		17-1616-LPS-CJB; D.I. 25 in Civil Action No. 17-1623-LPS-CJB), will be modified as follows with regard to this dispute: (1) The parties shall file a joint "Motion for Teleconference to Resolve Discovery Dispute," the text of which can be found in the "Forms" tab of Judge Burke's page on the District Court's website.; (2) A discovery dispute teleconference is set for 9/16/2019 at 02:00 PM before Judge Christopher J. Burke. (3) By no later than 9/5/2019, any party seeking relief shall file with the Court a letter, not to exceed three (3) pages, in no less than 12-point font, outlining the issues in dispute and its position on those issues. By no later than 9/11/2019, any party opposing the application for relief may file a letter, not to exceed three (3) pages, in no less than 12-point font, outlining that party(s) reasons for its opposition.; (4) Two courtesy copies of the letters are to be hand-delivered to the Clerk's Office within one hour of e-filing.; (5) The Court may choose to resolve the dispute prior to the telephone conference and will, in that event, cancel the conference.Ordered by Judge Christopher J. Burke on 8/29/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 08/29/2019)
08/29/2019	349	MOTION for Teleconference to Resolve Discovery Dispute - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 08/29/2019)
08/30/2019	350	REDACTED VERSION of 346 Letter, by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 08/30/2019)
09/03/2019	351	[SEALED] Letter to The Honorable Christopher J. Burke from John C. Phillips, Jr. regarding subsequent authority re: claim construction. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2)(Phillips, John) (Entered: 09/03/2019)
09/04/2019	352	Official Transcript of Telephone Conference held on July 23, 2019 before Judge Christopher J. Burke. Court Reporter Valerie Gunning, Telephone number (302) 573-6194. Transcript may be viewed at the court public terminal or purchased through the Court Reporter before the deadline for Release of Transcript Restriction. After that date, it may be obtained through PACER. Redaction Request due 9/25/2019. Redacted Transcript Deadline set for 10/7/2019. Release of Transcript Restriction set for 12/3/2019. (bpg) (Entered: 09/04/2019)
09/05/2019	353	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Discovery Dispute. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C)(Farnan, Brian) (Entered: 09/05/2019)
09/06/2019	354	REPORT AND RECOMMENDATION regarding claim construction. Please note that when filing Objections pursuant to Federal Rule of Civil Procedure 72 (b)(2), briefing consists solely of the Objections (no longer than ten (10) pages) and the Response to the Objections (no longer than ten (10) pages). No further briefing shall be permitted with respect to objections without leave of the Court. Objections to R&R due by 9/20/2019. Signed by Judge Christopher J. Burke on 9/6/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/06/2019)
09/09/2019	355	

		NOTICE OF SERVICE of [OUTSIDE ATTORNEYS' EYES ONLY] Non-Infringement Report of Olivier Harismendy, Ph.D. and [HIGHLY CONFIDENTIAL - ATTORNEYS' EYES ONLY] Rebuttal Expert Report of Justin V. Lewis filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 09/09/2019)
09/09/2019	356	NOTICE OF SERVICE of (i) Expert Rebuttal Report of Gregory Cooper, Ph.D. and (ii) Expert Rebuttal Report of Stephen L. Becker, Ph.D. filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 09/09/2019)
09/09/2019	357	Letter to The Honorable Christopher J. Burke from Michael J. Farnan regarding Response to PGDx's September 3, 2019 IPR Letter - re 351 Letter. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Exhibit C, # 4 Exhibit D, # 5 Exhibit E, # 6 Exhibit F, # 7 Exhibit G, # 8 Exhibit H)(Farnan, Michael) (Entered: 09/09/2019)
09/10/2019	358	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Supplemental Claim Construction Authority. (Attachments: # 1 Exhibit A, # 2 Exhibit B)(Farnan, Brian) (Entered: 09/10/2019)
09/11/2019	359	REPORT AND RECOMMENDATION regarding claim construction. Please note that when filing Objections pursuant to Federal Rule of Civil Procedure 72 (b)(2), briefing consists solely of the Objections (no longer than ten (10) pages) and the Response to the Objections (no longer than ten (10) pages). No further briefing shall be permitted with respect to objections without leave of the Court. Objections to R&R due by 9/25/2019. Signed by Judge Christopher J. Burke on 9/11/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/11/2019)
09/11/2019	360	REDACTED VERSION of 351 Letter by Personal Genome Diagnostics, Inc.. (Attachments: # 1 Exhibit 1-2)(Phillips, John) (Entered: 09/11/2019)
09/11/2019	361	[SEALED] Letter to the Honorable Christopher J. Burke from John C. Phillips, Jr. regarding Response to Plaintiffs' September 9, 2019 and September 10, 2019 Letters - re 358 Letter, 357 Letter,. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2)(Phillips, John) (Entered: 09/11/2019)
09/11/2019	362	[SEALED] Letter to The Honorable Christopher J. Burke from Karen Jacobs regarding Defendants response to Guardant Health's letter [D.I. 206, 353) - re (206 in 1:17-cv-01616-LPS-CJB, 353 in 1:17-cv-01623-LPS-CJB) Letter. (Attachments: # 1 Exhibit 1-7)(Jacobs, Karen) (Attachment 1 replaced on 9/12/2019) (dlb). (Entered: 09/11/2019)
09/12/2019	363	REDACTED VERSION of (206 in 1:17-cv-01616-LPS-CJB, 353 in 1:17-cv-01623-LPS-CJB) Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibits A-C)(Farnan, Brian) (Entered: 09/12/2019)
09/12/2019		CORRECTING ENTRY: The PDF for Exhibits attached to Letter at D.I. 362 has been replaced. (dlb) (Entered: 09/12/2019)
09/12/2019		Remark: The time for the Discovery Dispute Teleconference set for 9/16/2019 has been changed to commence at 4:00 P.M. The Court has set aside 45

		minutes for the call. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/12/2019)
09/13/2019	364	[SEALED] Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Declaration from Third Party Illumina Inc. - re (362 in 1:17-cv-01623-LPS-CJB, 213 in 1:17-cv-01616-LPS-CJB) Letter,. (Attachments: # 1 Illumina Declaration)(Tigan, Jeremy) (Entered: 09/13/2019)
09/16/2019	365	Official Transcript of Discovery Dispute Teleconference held on 08/05/19 before Judge Christopher J. Burke. Court Reporter/Transcriber Heather M. Triozzi,Telephone number 302-573-6195. Transcript may be viewed at the court public terminal or purchased through the Court Reporter/Transcriber before the deadline for Release of Transcript Restriction. After that date it may be obtained through PACER. Redaction Request due 10/7/2019. Redacted Transcript Deadline set for 10/17/2019. Release of Transcript Restriction set for 12/16/2019. (Triozzi, Heather) (Entered: 09/16/2019)
09/16/2019		Minute Entry for proceedings held before Judge Christopher J. Burke - Discovery dispute teleconference held on 9/16/2019 regarding Plaintiff's discovery dispute, (D.I. 203 in 17-1616-LPS-CJB; D.I. 349 in 17-1623-LPS-CJB). The Court took the matter under advisement. (Court Reporter Valerie Gunning. Clerk: M. Crawford) Appearances: B. Farnan, E. Reines, J. Constant for Plaintiff; J. Tigan, E. Marandett, M. Ives, R. Vallabhanen for Defendant Foundation Medicine, Inc.; J. Phillips, B. Zimmerman, S. Larson, J. Re for Defendant Personal Genome Diagnostics, Inc. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 09/16/2019)
09/17/2019	366	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Declaration of Dr. Helmy Eltoukhy. (Attachments: # 1 Attachment) (Farnan, Brian) (Entered: 09/17/2019)
09/17/2019	367	[SEALED] Letter to The Honorable Christopher J. Burke from Jeremy A. Tigan regarding Defendants Response to Submission of Declaration of Dr. Eltoukhy. (Attachments: # 1 Exhibit 1)(Tigan, Jeremy) (Entered: 09/17/2019)
09/17/2019	368	[SEALED] Letter to The Honorable Christopher J. Burke from Karen Jacobs regarding Defendants response to Guardant Health's letter CORRECTED/AMENDED - re (362 in 1:17-cv-01623-LPS-CJB, 213 in 1:17-cv-01616-LPS-CJB) Letter,. (Attachments: # 1 Exhibits 1-8)(Jacobs, Karen) (Entered: 09/17/2019)
09/18/2019	369	[SEALED] Letter to The Honorable Christopher J. Burke from Brian E. Farnan regarding Response to Defendants' September 17, 2019 Letter - re (367 in 1:17-cv-01623-LPS-CJB, 218 in 1:17-cv-01616-LPS-CJB) Letter. (Farnan, Brian) (Entered: 09/18/2019)
09/18/2019	370	ORAL ORDER: The Court hereby ORDERS as follows: (1) The Court has received the parties' supplemental letter briefs, (D.I. 217; D.I. 218; D.I. 221 in Civil Action No. 17-1616-LPS-CJB), filed without leave of Court following the September 16, 2019 discovery dispute teleconference regarding Plaintiff's discovery dispute motion, (D.I. 203 in Civil Action No. 17-1616-LPS-CJB). While the Court will accept these letters, the record on this motion is now

		closed, absent further leave of Court to file any additional letters regarding this motion. (2) No party may file a further supplemental letter regarding claim construction without leave of Court. Ordered by Judge Christopher J. Burke on 9/18/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/18/2019)
09/18/2019	371	REDACTED VERSION of (362 in 1:17-cv-01623-LPS-CJB, 213 in 1:17-cv-01616-LPS-CJB) Letter, *to The Honorable Christopher J. Burke from Karen Jacobs regarding Defendants response to Guardant Health's letter* by Foundation Medicine, Inc.. (Attachments: # 1 Exhibit 1-8)(Tigan, Jeremy) (Entered: 09/18/2019)
09/18/2019	372	STIPULATION to Amend Scheduling Order by Foundation Medicine, Inc.. (Tigan, Jeremy) (Entered: 09/18/2019)
09/18/2019	373	REDACTED VERSION of 361 Letter, by Personal Genome Diagnostics, Inc.. (Bilson, David) (Entered: 09/18/2019)
09/18/2019		SO ORDERED D.I. (224 in 1:17-cv-01616-LPS-CJB, 372 in 1:17-cv-01623-LPS-CJB) Stipulation to Amend Scheduling Order deadlines. Ordered by Judge Christopher J. Burke on 9/18/219. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/18/2019)
09/20/2019	374	REDACTED VERSION of 358 Letter by Guardant Health, Inc.. (Attachments: # 1 Exhibits A-B)(Farnan, Brian) (Entered: 09/20/2019)
09/24/2019	375	REDACTED VERSION of (217 in 1:17-cv-01616-LPS-CJB, 366 in 1:17-cv-01623-LPS-CJB) Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 09/24/2019)
09/25/2019	376	NOTICE OF SERVICE of (i) Expert Reply Report of Gregory Cooper, Ph.D. and (ii) Expert Reply Report of Stephen L. Becker, Ph.D. filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 09/25/2019)
09/25/2019	377	NOTICE OF SERVICE of (1) [CONFIDENTIAL - OUTSIDE ATTORNEYS' ONLY] Reply Expert Report of Olivier Harismendy, Ph.D.; and (2) [CONFIDENTIAL - OUTSIDE ATTORNEYS' EYES ONLY] Expert Reply Report of Bradley N. Reiff filed by Personal Genome Diagnostics, Inc..(Bilson, David) (Entered: 09/25/2019)
09/25/2019	378	[SEALED] OBJECTIONS by Foundation Medicine, Inc., Personal Genome Diagnostics, Inc. to (359 in 1:17-cv-01623-LPS-CJB) REPORT AND RECOMMENDATIONS. Please note that when filing Objections pursuant to Federal Rule of Civil Procedure 72(b)(2), briefing consists solely of the Objections (no longer than ten (10) pages) and the Response to the Objections (no longer than ten . (Attachments: # 1 Certification for Objections)(Phillips, John) (Entered: 09/25/2019)
09/27/2019	379	Letter to The Honorable Leonard P. Stark from John C. Phillips, Jr. regarding Report & Recommendation Docket Items - re (378 in 1:17-cv-01623-LPS-CJB) Objections,. (Phillips, John) (Entered: 09/27/2019)
09/30/2019	380	ORAL ORDER: Due to a scheduling conflict, the Court hereby ORDERS that the hearing on case dispositive and Daubert motions scheduled for January 24,

		2020 is rescheduled to January 23, 2020 at 11:00a.m. in Courtroom 2A. Ordered by Judge Christopher J. Burke on 9/30/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(dlb) (Entered: 09/30/2019)
09/30/2019	381	REDACTED VERSION of (221 in 1:17-cv-01616-LPS-CJB, 369 in 1:17-cv-01623-LPS-CJB) Letter by Guardant Health, Inc.. (Farnan, Brian) (Entered: 09/30/2019)
10/01/2019	382	MOTION for Pro Hac Vice Appearance of Attorney Eric S. Hochstadt - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke.(Farnan, Brian) (Entered: 10/01/2019)
10/02/2019		SO ORDERED D.I. 382 MOTION for Pro Hac Vice Appearance of Attorney Eric S. Hochstadt filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 10/2/2019. (dlb) (Entered: 10/02/2019)
10/02/2019		Pro Hac Vice Attorney Eric S. Hochstadt for Guardant Health, Inc. added for electronic noticing. Pursuant to Local Rule 83.5 (d), Delaware counsel shall be the registered users of CM/ECF and shall be required to file all papers. (sam) (Entered: 10/02/2019)
10/03/2019	383	REDACTED VERSION of (228 in 1:17-cv-01616-LPS-CJB, 378 in 1:17-cv-01623-LPS-CJB) Objections, by Foundation Medicine, Inc.. (Attachments: # 1 Certification for Objections)(Bilson, David) (Entered: 10/03/2019)
10/03/2019	384	NOTICE to Take Deposition of Stephen L. Becker, Ph.D. on November 5-7, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 10/03/2019)
10/03/2019	385	NOTICE to Take Deposition of Gregory Cooper, Ph.D. on October 15-17, 2019 filed by Personal Genome Diagnostics, Inc..(Phillips, John) (Entered: 10/03/2019)
10/04/2019	386	NOTICE to Take Deposition of Bradley Reiff on October 23, 2019 filed by Guardant Health, Inc..(Farnan, Brian) (Entered: 10/04/2019)
10/09/2019	387	[SEALED] RESPONSE TO OBJECTIONS by Guardant Health, Inc. re (228 in 1:17-cv-01616-LPS-CJB, 378 in 1:17-cv-01623-LPS-CJB) Objections, . (Farnan, Brian) (Entered: 10/09/2019)
10/09/2019	388	[SEALED] DECLARATION re (237 in 1:17-cv-01616-LPS-CJB, 387 in 1:17-cv-01623-LPS-CJB) Response to Objections *of Derek Walter* by Guardant Health, Inc.. (Attachments: # 1 Exhibit 1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4)(Farnan, Brian) (Entered: 10/09/2019)
10/11/2019	389	REPORT AND RECOMMENDATION regarding claim construction. Please note that when filing Objections pursuant to Federal Rule of Civil Procedure 72 (b)(2), briefing consists solely of the Objections (no longer than ten (10) pages) and the Response to the Objections (no longer than ten (10) pages). No further briefing shall be permitted with respect to objections without leave of the Court. Objections to R&R due by 10/25/2019. Signed by Judge Christopher J. Burke on 10/11/2019. Associated Cases: 1:17-cv-01616-LPS-CJB, 1:17-cv-01623-LPS-CJB(mlc) (Entered: 10/11/2019)

10/14/2019	390	MOTION for Pro Hac Vice Appearance of Attorney Doug W. McClellan - filed by Guardant Health, Inc.. Motions referred to Christopher J. Burke. (Farnan, Brian) (Entered: 10/14/2019)
10/16/2019	391	NOTICE of Amendment to Third-Party Subpoena to Wilson, Sonsini, Goodrich & Rosati by Personal Genome Diagnostics, Inc. (Attachments: # 1 Exhibit A)(Bilson, David) (Entered: 10/16/2019)
10/16/2019	392	NOTICE of Amendment to Third-Party Subpoena to Vern Norviel by Personal Genome Diagnostics, Inc. (Attachments: # 1 Exhibit A)(Bilson, David) (Entered: 10/16/2019)
10/16/2019	393	REQUEST for Oral Argument by Personal Genome Diagnostics, Inc.. (Phillips, John) (Entered: 10/16/2019)
10/17/2019	394	REDACTED VERSION of (237 in 1:17-cv-01616-LPS-CJB, 387 in 1:17-cv-01623-LPS-CJB) Response to Objections by Guardant Health, Inc.. (Farnan, Brian) (Entered: 10/17/2019)
10/17/2019	395	REDACTED VERSION of (388 in 1:17-cv-01623-LPS-CJB, 238 in 1:17-cv-01616-LPS-CJB) Declaration, *of Derek Walter* by Guardant Health, Inc.. (Attachments: # 1 Exhibits 1-4)(Farnan, Brian) (Entered: 10/17/2019)
10/21/2019		SO ORDERED D.I. 390 MOTION for Pro Hac Vice Appearance of Attorney Doug W. McClellan filed by Guardant Health, Inc. Ordered by Judge Christopher J. Burke on 10/21/2019. (dlb) (Entered: 10/21/2019)

PACER Service Center			
Transaction Receipt			
10/21/2019 19:09:20			
PACER Login:	wg0135:2661645:0	**Client Code:**	51042.0004-f203
Description:	Docket Report	**Search Criteria:**	1:17-cv-01623-LPS-CJB Start date: 1/1/1970 End date: 10/21/2019
Billable Pages:	30	**Cost:**	3.00

Electronic Acknowledgement Receipt

EFS ID:	37531956
Application Number:	16575128
International Application Number:	
Confirmation Number:	9440
Title of Invention:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-704.313
Receipt Date:	22-OCT-2019
Filing Date:	
Time Stamp:	20:02:48
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	Notice of concurrent proceedings / decisions	2019-10-22_GH0002US-CON14_NtcConcurrentProceedings.pdf	68251 23847c583eac303a12100115138bffb75790b279	no	2

Warnings:

Information:					
2	Notice of concurrent proceedings / decisions	2019-10-22_GH0002US-CON14_NtcConcurrentProceedings_IC.pdf	83538 d9d4d0d4302ad7605a6446d9133ec084b81076b5	no	2
Warnings:					
Information:					
3	Notice of concurrent proceedings / decisions	2019-10-22_GH0002US-CON14_NtcConcurrentProceedings_IV.pdf	1033607 af6c07b9d4ae974dc6c01a08f9a368835d0ace3f	no	99
Warnings:					
Information:					
		Total Files Size (in bytes):	1185396		

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

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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
16/575,128	09/18/2019	AmirAli TALASAZ	42534-704.313

CONFIRMATION NO. 9440

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

FORMALITIES LETTER

OC000000113168719

Date Mailed: 12/09/2019

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing.

Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- Additional claim fees of $ **6220** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **6400** for **64** total claims over 20.
- $ **820** for multiple dependent claim surcharge.
- $(**1000**) previous unapplied payment amount.
- $ **6220** TOTAL FEE BALANCE DUE.

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

Replies should be mailed to:

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

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

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

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

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

/mordonez/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/575,128

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			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	84 minus 20 =	* 64			OR	x 100 =	6400
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 460 =	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))							820
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	8940

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	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	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest 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
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/575,128	09/18/2019	1636	2720	42534-704.313	30	3

CONFIRMATION NO. 9440

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

FILING RECEIPT

OC000000113168718

Date Mailed: 12/09/2019

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

AmirAli TALASAZ, Atherton, CA;

Applicant(s)

GUARDANT HEALTH, INC., Redwood City, CA;

Power of Attorney: The patent practitioners associated with Customer Number 115823

Domestic Priority data as claimed by applicant

This application is a CON of 16/283,635 02/22/2019 PAT 10494678
which is a CON of 15/872,831 01/16/2018 PAT 10457995
which is a CON of 15/828,099 11/30/2017
which is a CON of 15/467,570 03/23/2017 PAT 9840743
which is a CON of 14/425,189 03/02/2015 PAT 10041127
which is a 371 of PCT/US2013/058061 09/04/2013
which claims benefit of 61/845,987 07/13/2013
and claims benefit of 61/793,997 03/15/2013
and claims benefit of 61/704,400 09/21/2012
and claims benefit of 61/696,734 09/04/2012

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: 10/02/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/575,128**

Projected Publication Date: 03/19/2020

Non-Publication Request: No

Early Publication Request: No

Title

SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

Preliminary Class

435

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

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

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
16575128	

Applicant(s) AmirAli TALASAZ

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
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Total Indep	3		0		0	
Total Depend	79		0		0	
Total Claims	82		0		0	

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To: Patents@guardanthealth.com,patentdocket@wsgr.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 115823

Dec 09, 2019 03:29:15 AM

Dear PAIR Customer:

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 115823 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
16575128	NTC.MISS.PRT	12/09/2019	42534-704.313
	APP.FILE.REC	12/09/2019	42534-704.313

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Document Code: IMIS

Notice of Fee Due

Application Number: 16575128 Date: 12/06/19

Fees are due for the application or document dated 09/18/2019 The payment was not collectable for the reason indicated below.

Note: If the fee due is for any of the filing fees, the surcharge for late payment of the filing fees is now due as well.

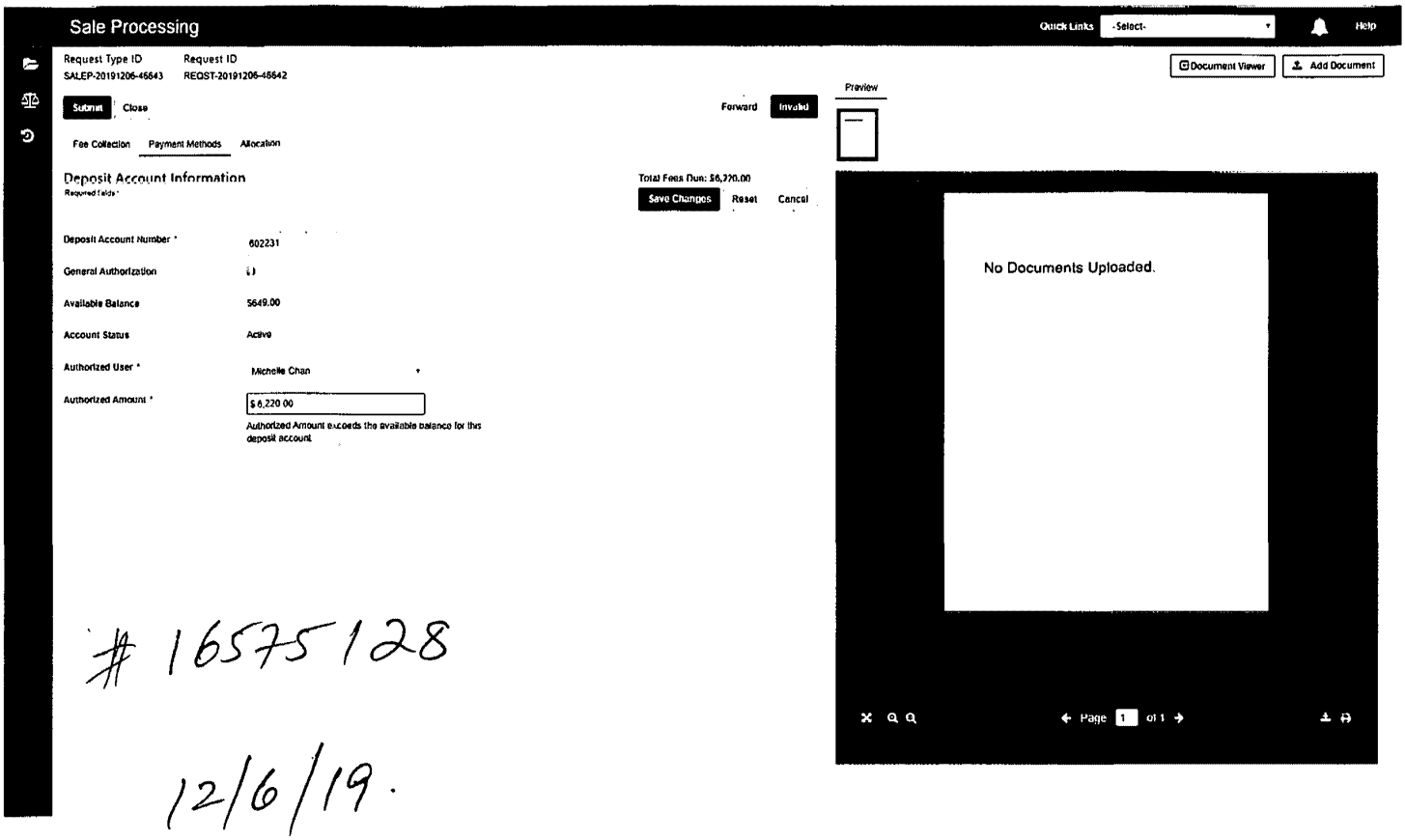
- ☐ Insufficient payment by check or money order.
- ☐ No authorization to charge a deposit account.
- ☐ Invalid deposit account number.
- ☐ User name not listed in deposit account at (time).
- ☑ Insufficient funds in deposit account 602231 at 11:50AM (time).
- ☐ Insufficient payment by credit card.
- ☐ Declined credit card : (time).

Fee code(s) to be applied:	1202	5400
	1203	820
Amount in holding fee code:		
	1622/2622	
	1999	

Total remaining due from applicant: $6220

RAM Operator Eleni Wodaje

Rev. 04/10/2013



16575128

12/6/19.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli Talasaz Serial Number: 16/575,128 Filing Date: September 18, 2019 Title: SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION	Confirmation No.: 9440 Customer No.: 115823 Group Art Unit: 1637 Examiner: To be assigned

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

RESPONSE TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION AND PRELIMINARY AMENDMENT

Sir:

This paper is in response to the Notice to File Corrected Application Papers mailed on December 9, 2019. The shortened statutory period for reply expires February 9, 2020; therefore, this response is timely filed. Applicant respectfully requests consideration of the above-referenced application in view of the following amendments and remarks:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

Electronic Acknowledgement Receipt

EFS ID:	38333551
Application Number:	16575128
International Application Number:	
Confirmation Number:	9440
Title of Invention:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-704.313
Receipt Date:	17-JAN-2020
Filing Date:	18-SEP-2019
Time Stamp:	17:05:14
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		2020-01-17_GH0002US-CON14_MPResponse.pdf	108165 f04fd3bcc4e98db07ae507c860efa6e52ca4ff7d	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Arguments/Remarks Made in an Amendment	6	6
	Claims	2	5
	Applicant Response to Pre-Exam Formalities Notice	1	1
Warnings:			
Information:			
	Total Files Size (in bytes):	108165	

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.

REMARKS

Claims 1-30 were previously pending, but are hereby cancelled without disclaimer or prejudice. Claims 31-60 are newly added. Support for the new claims may be found throughout the application as filed, for example, at least at paragraphs [0024], [0067], [0071], and [00150]. No new matter is added by these amendments. Thus, claims 31-60 are now pending and ready for examination.

Based on the aforementioned amendments to the claims, no additional claim fees are due.

CONCLUSION

Applicant believes that the present application is now in condition for examination and respectfully requests that the Examiner expedite the prosecution of this application to allowance. The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0002US-CON14).

Respectfully submitted,
GUARDANT HEALTH, INC.

Date: January 17, 2020 By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1. - 30. (Cancelled).

31. (New): A method for inferring a quantitative measure of microsatellite changes in a sample of cell-free nucleic acid molecules from a subject having a cancer or suspected of having a cancer, the method comprising:

(a) non-uniquely tagging a plurality of the cell-free nucleic acid molecules from the sample with molecular barcodes from a set of molecular barcodes to produce a set of tagged parent polynucleotides;

(b) amplifying a plurality of the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;

(c) sequencing a plurality of the amplified tagged progeny polynucleotides to produce a set of sequencing reads;

(d) grouping a plurality of sequencing reads from the set of sequencing reads into families, each family having sequencing reads amplified from the same tagged parent polynucleotide;

(e) determining a quantitative measure of sequence reads in each family and a quantitative measure of unique families;

(f) inferring a measure of tagged parent polynucleotides in the set of tagged parent polynucleotides based on the quantitative measure of the sequence reads in each family and the quantitative measure of unique families;

(g) determining a quantitative measure of microsatellite changes from among the families; and

(h) based on the determined quantitative measure of microsatellite changes from among the families, inferring a quantitative measure of microsatellite changes in the number of inferred tagged parent polynucleotides.

32. (New): The method of claim 31, wherein the sample is a bodily fluid sample selected from the group consisting of blood, plasma, and serum.
33. (New): The method of claim 31, wherein a molecular barcode from the set of molecular barcodes is attached on both ends of a molecule of the cell-free nucleic acid molecules.
34. (New): The method of claim 31, wherein the molecular barcodes from the set of molecular barcodes have 2 to 1,000 different molecular barcode sequences.
35. (New): The method of claim 31, wherein non-unique tagging comprises performing blunt-end ligation or sticky-end ligation.
36. (New): The method of claim 31, further comprising selectively enriching the amplified tagged progeny polynucleotides for target regions associated with cancer prior to sequencing.
37. (New): The method of claim 31, further comprising filtering out sequencing reads that fail to meet a quality threshold.
38. (New): The method of claim 31, further comprising mapping a plurality of sequencing reads from the set of sequencing reads to a reference sequence.
39. (New): The method of claim 38, wherein the grouping is based on a combination of sequence information of the molecular barcodes and beginning and end base positions of the sequencing reads that map to the reference sequence.
40. (New): The method of claim 31, further comprising collapsing the sequencing reads in a plurality of families to generate consensus sequence reads.
41. (New): The method of claim 40, further comprising identifying one or more consensus sequence reads having a somatic mutation as compared to a reference sequence.
42. (New): The method of claim 31, further comprising reporting a treatment regimen based on the inferred quantitative measure of microsatellite changes in the number of inferred tagged parent polynucleotides.

43. (New): A method for detecting a genetic variation in one or more microsatellite regions in a sample of cell-free nucleic acid molecules from a subject having a cancer or suspected of having a cancer, the method comprising:
    (a) ligating molecular barcodes from a set of molecular barcodes having 2 to 1,000,000 different molecular barcode sequences to a population of cell-free nucleic acids obtained from the sample to produce tagged parent polynucleotides;
    (b) amplifying the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;
    (c) sequencing a plurality of the amplified tagged progeny polynucleotides to produce a set of sequencing reads; and
    (d) determining, from among the sequencing reads in the set of sequencing reads, a quantitative measure of polymorphic forms comprising microsatellite changes in the one or more microsatellite regions, thereby detecting the genetic variation in the one or more microsatellite regions.
44. (New): The method of claim 43, wherein the genetic variation in the one or more microsatellite regions comprises an insertion or deletion (indel).
45. (New): The method of claim 43, wherein the sample is a bodily fluid sample selected from the group consisting of blood, plasma, and serum.
46. (New): The method of claim 43, wherein a molecular barcode from the set of molecular barcodes is attached on both ends of a molecule of the cell-free nucleic acid molecules.
47. (New): The method of claim 43, wherein the set of molecular barcodes comprises molecular barcodes having 2 to 1,000 different molecular barcode sequences.
48. (New): The method of claim 43, wherein the molecular barcodes are ligated to the cell-free nucleic acid molecules by blunt-end ligation or sticky-end ligation.
49. (New): The method of claim 43, further comprising selectively enriching the amplified tagged progeny polynucleotides for target regions associated with cancer prior to sequencing.
50. (New): The method of claim 43, further comprising filtering out sequencing reads that fail to meet a quality threshold.
51. (New): The method of claim 43, further comprising mapping a plurality of sequencing reads from the set of sequencing reads to a reference sequence.

52. (New): The method of claim 51, further comprising grouping a subset of sequencing reads into a plurality of families based on sequence information of the molecular barcodes and beginning and end base positions of the sequencing reads that map to the reference sequence.
53. (New): The method of claim 43, further comprising collapsing the sequencing reads in a plurality of families to generate consensus sequence reads.
54. (New): The method of claim 53, further comprising identifying one or more consensus sequence reads having the genetic variation as compared to a reference sequence.
55. (New): The method of claim 43, wherein the population of cell-free nucleic acids comprises 1 nanogram (ng) to 100 ng of cell-free nucleic acid molecules.
56. (New): The method of claim 43, wherein the cell-free nucleic acids are cell-free deoxyribonucleic acid (cfDNA) molecules.
57. (New): The method of claim 56, wherein the cfDNA is double-stranded DNA.
58. (New): The method of claim 43, further comprising determining a confidence score based on the presence or absence of the genetic variation detected in the one or more microsatellite regions.
59. (New): The method of claim 43, further comprising reporting a treatment regimen based on the quantitative measure of polymorphic forms comprising microsatellite changes in the one or more microsatellite regions.
60. (New): The method of claim 59, further comprising administering the treatment regimen to the subject.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/575,128

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			N/A	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 460 =	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			TOTAL	2720

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/575,128	09/18/2019	1637	2720	42534-704.313	30	2

CONFIRMATION NO. 9440

UPDATED FILING RECEIPT

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

OC000000114101780

Date Mailed: 01/23/2020

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

AmirAli TALASAZ, Atherton, CA;

Applicant(s)

GUARDANT HEALTH, INC., Redwood City, CA;

Power of Attorney: The patent practitioners associated with Customer Number 115823

Domestic Priority data as claimed by applicant

This application is a CON of 16/283,635 02/22/2019 PAT 10494678
which is a CON of 15/872,831 01/16/2018 PAT 10457995
which is a CON of 15/828,099 11/30/2017
which is a CON of 15/467,570 03/23/2017 PAT 9840743
which is a CON of 14/425,189 03/02/2015 PAT 10041127
which is a 371 of PCT/US2013/058061 09/04/2013
which claims benefit of 61/845,987 07/13/2013
and claims benefit of 61/793,997 03/15/2013
and claims benefit of 61/704,400 09/21/2012
and claims benefit of 61/696,734 09/04/2012

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: 10/02/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/575,128**

Projected Publication Date: 03/19/2020

Non-Publication Request: No

Early Publication Request: No

Title

SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

Preliminary Class

506

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

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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.

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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To: Patents@guardanthealth.com,patentdocket@wsgr.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 115823

Jan 24, 2020 03:33:11 AM

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Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
16575128	APP.FILE.REC	01/23/2020	42534-704.313

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/575,128	09/18/2019	AmirAli TALASAZ	42534-704.313	9440

115823 7590 01/29/2020

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
BENZION, GARY	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
01/29/2020	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):

Patents@guardanthealth.com
patentdocket@wsgr.com

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/575,128	**Applicant(s)** TALASAZ, AmirAli	
	Examiner Liana Walsh	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 18 September 2019 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   - A. ☑ for an original nonprovisional application (Track I).
   - B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:
   - A. filing a **petition for extension of time** to extend the time period for filing a reply;
   - B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;
   - C. filing a **request for continued examination** ;
   - D. filing a notice of appeal;
   - E. filing a request for suspension of action;
   - F. mailing of a notice of allowance;
   - G. mailing of a final Office action;
   - H. completion of examination as defined in 37 CFR 41.102; or
   - I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Liana Walsh at (571)272-3206.

In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/LIANA S WALSH/ Lead Paralegal Specialist, OPET	

To: Patents@guardanthealth.com,patentdocket@wsgr.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 115823

Jan 31, 2020 03:42:29 AM

Dear PAIR Customer:

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
16575128	TRACK1.GRANT	01/29/2020	42534-704.313

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Thank you for prompt attention to this notice,

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/575,128	09/18/2019	AmirAli TALASAZ	42534-704.313	9440

115823 7590 02/14/2020

Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

EXAMINER	
HORLICK, KENNETH R	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
02/14/2020	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents@guardanthealth.com
patentdocket@wsgr.com

Office Action Summary	Application No. 16/575,128	Applicant(s) TALASAZ, AmirAli	
	Examiner KENNETH R HORLICK	Art Unit 1637	AIA (FITF) Status Yes

-- 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 _____.

☐ 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) 31-60 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) 31-60 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 9/18/19 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 See Continuation Sheet.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Continuation of Attachment(s) 2) Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date: 10/18/19; 10/18/19; 10/18/19; 10/18/19; 10/18/19; 10/18/19; 10/18/19.

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

OBJECTION

2. The specification is objected to because of the following informality: the continuation information must be updated to reflect the current status of all of the parent applications.

NON-PRIOR ART REJECTIONS

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

4. Claims 31-60 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 10,494,678 in view of Sacko et al. (US 2010/0264331).

The patented claims are generic with respect to the instant claims, reciting the genus 'somatic genetic variants', while the instant claims require the species 'microsatellite changes'.

Sacko et al. discloses that cell-free nucleic acids from blood of cancer patients are associated with microsatellite mutations and instabilities (see paragraph 0005).

One of ordinary skill in the art considering the patented methods would have been motivated to modify them by applying them to microsatellite changes because Sacko et al. disclosed that microsatellite changes were known to occur in cell-free nucleic acids from blood of cancer patients.

5. Claims 31-60 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 9,902,992 in view of Sacko et al. (US 2010/0264331).

The patented claims are generic with respect to the instant claims, reciting the genus 'genetic aberrations', while the instant claims require the species 'microsatellite changes'.

Sacko et al. discloses that cell-free nucleic acids from blood of cancer patients are associated with microsatellite mutations and instabilities (see paragraph 0005).

One of ordinary skill in the art considering the patented methods would have been motivated to modify them by applying them to microsatellite changes because Sacko et al. disclosed that microsatellite changes were known to occur in cell-free nucleic acids from blood of cancer patients.

6. Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 78, 207-211, 214-222, and 224-226 of copending Application No. 15/828,099 in view of Sacko et al. (US 2010/0264331).

The copending claims are generic with respect to the instant claims, reciting the genus 'somatic genetic variant', while the instant claims require the species 'microsatellite changes'.

Sacko et al. discloses that cell-free nucleic acids from blood of cancer patients are associated with microsatellite mutations and instabilities (see paragraph 0005).

One of ordinary skill in the art considering the copending methods would have been motivated to modify them by applying them to microsatellite changes because Sacko et al. disclosed that microsatellite changes were known to occur in cell-free nucleic acids from blood of cancer patients.

This is a provisional nonstatutory double patenting rejection.

7. Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31-48 and 51-60 of copending Application No. 16/283,629 in view of Sacko et al. (US 2010/0264331).

The copending claims are generic with respect to the instant claims, reciting the genus 'somatic genetic variants', while the instant claims require the species 'microsatellite changes'.

Sacko et al. discloses that cell-free nucleic acids from blood of cancer patients are associated with microsatellite mutations and instabilities (see paragraph 0005).

One of ordinary skill in the art considering the copending methods would have been motivated to modify them by applying them to microsatellite changes because Sacko et al. disclosed that microsatellite changes were known to occur in cell-free nucleic acids from blood of cancer patients.

This is a provisional nonstatutory double patenting rejection.

8. Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31-33, 35-38, 41-43, and 45-64 of copending Application No. 16/575,079 in view of Sacko et al. (US 2010/0264331).

The copending claims are generic with respect to the instant claims, reciting the genus 'somatic genetic variants', while the instant claims require the species 'microsatellite changes'.

Sacko et al. discloses that cell-free nucleic acids from blood of cancer patients are associated with microsatellite mutations and instabilities (see paragraph 0005).

One of ordinary skill in the art considering the copending methods would have been motivated to modify them by applying them to microsatellite changes because Sacko et al. disclosed that microsatellite changes were known to occur in cell-free nucleic acids from blood of cancer patients.

This is a provisional nonstatutory double patenting rejection.

9. Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31-60 of copending Application No. 16/593,633 in view of Sacko et al. (US 2010/0264331).

The copending claims are generic with respect to the instant claims, reciting the genus 'somatic genetic variants', while the instant claims require the species 'microsatellite changes'.

Sacko et al. discloses that cell-free nucleic acids from blood of cancer patients are associated with microsatellite mutations and instabilities (see paragraph 0005).

One of ordinary skill in the art considering the copending methods would have been motivated to modify them by applying them to microsatellite changes because Sacko et al. disclosed that microsatellite changes were known to occur in cell-free nucleic acids from blood of cancer patients.

This is a provisional nonstatutory double patenting rejection.

10. Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 31-60 of copending Application No. 16/593,653 in view of Sacko et al. (US 2010/0264331).

The copending claims are generic with respect to the instant claims, reciting the genus 'somatic genetic variants', while the instant claims require the species 'microsatellite changes'.

Sacko et al. discloses that cell-free nucleic acids from blood of cancer patients are associated with microsatellite mutations and instabilities (see paragraph 0005).

One of ordinary skill in the art considering the copending methods would have been motivated to modify them by applying them to microsatellite changes because Sacko et al. disclosed that microsatellite changes were known to occur in cell-free nucleic acids from blood of cancer patients.

This is a provisional nonstatutory double patenting rejection.

CONCLUSION

11. Claims 31-60 are free of the prior art, but are rejected for another reason. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENNETH R HORLICK whose telephone number is (571)272-0784. The examiner can normally be reached on Mon. - Thurs. 8:30 - 6:30.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

02/10/20

/KENNETH R HORLICK/
Primary Examiner, Art Unit 1637

Notice of References Cited	Application/Control No. 16/575,128	Applicant(s)/Patent Under Reexamination TALASAZ, AmirAli	
	Examiner KENNETH R HORLICK	Art Unit 1637	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-20100264331-A1	10-2010	Sacko; Mory	G01N21/6428	250/459.1
	B					
	C					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
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NON-PATENT DOCUMENTS

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Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/575,128	TALASAZ, AmirAli
	Examiner	Art Unit
	KENNETH R HORLICK	1637

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* 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
inventor name search	02/11/2020	KH
updated parent searches in USPAT and PGPUB	02/11/2020	KH
reviewed parent applications and references therein	02/11/2020	KH

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

/KENNETH R HORLICK/ Primary Examiner, Art Unit 1637	

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BIB DATA SHEET

CONFIRMATION NO. 9440

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
16/575,128	09/18/2019 RULE	435	1637	42534-704.313

APPLICANTS
GUARDANT HEALTH, INC., Redwood City, CA;

INVENTORS
AmirAli TALASAZ, Atherton, CA;

**** CONTINUING DATA ***************************
This application is a CON of 16/283,635 02/22/2019 PAT 10494678
which is a CON of 15/872,831 01/16/2018 PAT 10457995
which is a CON of 15/828,099 11/30/2017
which is a CON of 15/467,570 03/23/2017 PAT 9840743
which is a CON of 14/425,189 03/02/2015 PAT 10041127
which is a 371 of PCT/US2013/058061 09/04/2013
which claims benefit of 61/845,987 07/13/2013
and claims benefit of 61/793,997 03/15/2013
and claims benefit of 61/704,400 09/21/2012
and claims benefit of 61/696,734 09/04/2012

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
10/02/2019

Foreign Priority claimed ❑ Yes ☑ No 35 USC 119(a-d) conditions met ❑ Yes ☑ No Verified and Acknowledged /KENNETH R HORLICK/ Examiner's Signature	❑ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	16	30	2

ADDRESS
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304
UNITED STATES

TITLE
SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

FILING FEE RECEIVED		
2720	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

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

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16575128
Filing Date	2019-09-18
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-704.313

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	1	2013159035	WO	A2	2013-10-24	Mitchell et al.		
	2	2013173394	WO	A2	2013-11-21	Wang et al.		
	3	2013181170	WO	A1	2013-12-05	OTWINOWSKI et al.	Entire Document	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.R.H/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

	4	2013188471	WO	A2	2013-12-19	Faham et al.		
	5	2013190441	WO	A2	2013-12-27	CHIU et al.	Entire Document	
	6	2014004726	WO	A1	2014-01-03	Chen et al.		
	7	2014014497	WO	A1	2014-01-23	Rava et al.		
	8	2014015319	WO	A1	2014-01-23	Rava		
	9	2014039556	WO	A1	2014-03-13	TALASAZ et al.	Entire Document	
	10	2014093330	WO	A1	2014-06-19	Raymond et al.		
	11	2014145078	WO	A1	2014-09-18	Srinivasan et al.		
	12	2014151117	WO	A1	2014-09-25	Diehn et al.	Entire Document	
	13	2014152990	WO	A1	2014-09-25	SPENCE et al.		
	14	2015159293	WO	A2	2015-10-22	DOR et al.	Entire Document	

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	First Named Inventor	AmirAli TALASAZ
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	Examiner Name	
	Attorney Docket Number	42534-704.313

	15	2016015058	WO	A2	2016-01-28	Shendure et al.	Entire Document	
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	18	2017181146	WO	A1	2017-10-19	MORTIMER et al.	Entire Document	

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	DE SAIZIEU, et al. "Bacterial transcript imaging by hybridization of total RNA to oligonucleotide arrays." Nature Biotechnology, 16: 45-48 (1998).	
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	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

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	Application Number	16575128
	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

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	34	Guardant Health vs. FMI 1st Amended Answer to Second Amended Complaint dated May 6, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	35	Guardant Health vs. FMI Invalidity Contentions dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	36	Guardant Health vs. FMI Invalidity Exhibit A-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	37	Guardant Health vs. FMI Invalidity Exhibit A-2, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	38	Guardant Health vs. FMI Invalidity Exhibit A-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	

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	39	Guardant Health vs. FMI Invalidity Exhibit A-8, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	40	Guardant Health vs. FMI Invalidity Exhibit B-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	41	Guardant Health vs. FMI Invalidity Exhibit B-2, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	42	Guardant Health vs. FMI Invalidity Exhibit B-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	43	Guardant Health vs. FMI Invalidity Exhibit B-7, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	44	Guardant Health vs. FMI Invalidity Exhibit C-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	45	Guardant Health vs. FMI Invalidity Exhibit C-11, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
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	47	Guardant Health vs. FMI Invalidity Exhibit C-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	48	Guardant Health vs. FMI Invalidity Exhibit C-4, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	49	Guardant Health vs. FMI Invalidity Exhibit C-5, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	

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	50	Guardant Health vs. FMI Invalidity Exhibit D-1, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	

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See attached certification statement.

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

☒ A certification statement is not submitted herewith.

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

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-10-18
Name/Print	Timothy A. Hott	Registration Number	67740

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16575128
Filing Date	2019-09-18
First Named Inventor	AmirAli TALASAZ
Art Unit	
Examiner Name	
Attorney Docket Number	42534-704.313

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	1	Guardant Health vs. FMI Invalidity Exhibit D-2, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	2	Guardant Health vs. FMI Invalidity Exhibit D-3, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	3	Guardant Health vs. FMI Invalidity Exhibit D-5, dated June 25, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	4	Guardant Health vs. FMI Second Amended Complaint dated March 6, 2018 (C.A. No. 17-cv-1616-LPS-CJB)	
	5	Guardant Health vs. FMI Suppl Invalidity References dated February 15, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	6	Guardant Health vs. FMI Supplemental Invalidity Contentions dated March 29, 2019 (C.A. No. 17-cv-1616-LPS-CJB)	
	7	Guardant Health vs. PGDx Amended Answer to Second Amended Complaint dated April 30, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	8	Guardant Health vs. PGDx Invalidity Claim Chart A, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	9	Guardant Health vs. PGDx Invalidity Claim Chart B, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	10	Guardant Health vs. PGDx Invalidity Claim Chart C, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	11	Guardant Health vs. PGDx Invalidity Claim Chart D, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	

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	12	Guardant Health vs. PGDx Invalidity Claim Chart E, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	13	Guardant Health vs. PGDx Invalidity Claim Chart F, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	14	Guardant Health vs. PGDx Invalidity Claim Chart G, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	15	Guardant Health vs. PGDx Invalidity Claim Chart H, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	16	Guardant Health vs. PGDx Invalidity Claim Chart I, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	17	Guardant Health vs. PGDx Invalidity Claim Chart J, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	18	Guardant Health vs. PGDx Invalidity Claim Chart K, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	19	Guardant Health vs. PGDx Invalidity Claim Chart L, dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	
	20	Guardant Health vs. PGDx Invalidity Contentions dated June 25, 2018 (C.A. No. 17-cv-1623-LPS-CJB)	
	21	Guardant Health vs. PGDx Second Amended Complaint dated March 23, 2018 (C.A. No. 17-cv-1623-LPS-CJB)	
	22	Guardant Health vs. PGDx Second Updated Invalidity Contentions dated May 13, 2019 (C.A. No. 17-cv-1623-LPS-CJB)	

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Examiner Signature	/KENNETH R HORLICK/	Date Considered	02/07/2020

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

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See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-10-18
Name/Print	Timothy A. Hott	Registration Number	67740

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

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

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Name/Print	Timothy A. Hott	Registration Number	67740

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2019-09-18
	First Named Inventor	AmirAli TALASAZ
	Art Unit	
	Examiner Name	
	Attorney Docket Number	42534-704.313

CERTIFICATION STATEMENT

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2019-10-18
Name/Print	Timothy A. Hott	Registration Number	67740

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First Named Inventor	AmirAli TALASAZ
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Attorney Docket Number	42534-704.313

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/575,128	09/18/2019	AmirAli TALASAZ	42534-704.313

CONFIRMATION NO. 9440

115823
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

PUBLICATION NOTICE

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Title:SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

Publication No.US-2020-0087735-A1
Publication Date:03/19/2020

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Mar 20, 2020 09:45:51 AM

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650 Page Mill Road
Palo Alto, CA 94304
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Application	Document	Mailroom Date	Attorney Docket No.
16575128	NTC.PUB	03/19/2020	42534-704.313

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Doc Code: DIST.E.FILE **Document Description: Electronic Terminal Disclaimer - Filed**	PTO/SB/25 PTO/SB/26 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION AND TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT**
Application Number	16575128
Filing Date	18-Sep-2019
First Named Inventor	AmirAli TALASAZ
Attorney Docket Number	42534-704.313
Title of Invention	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
GUARDANT HEALTH, INC.	100 %

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

15828099 filed on 11/30/2017

16575079 filed on 09/18/2019

16593633 filed on 10/04/2019

16593653 filed on 10/04/2019

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) with percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

9902992

10494678

10501810

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and 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 owner 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.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.

Applicants claims the following fee status:

○ Small Entity

○ Micro Entity

◉ Regular Undiscounted

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES

I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Registration Number 67740

○ A sole inventor

○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application

○ A joint inventor; all of whom are signing this request

Signature	/Timothy A. Hott/
Name	Timothy A. Hott

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16575128
Filing Date:	18-Sep-2019
Title of Invention:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Filer:	Timothy A Hott/Michelle Chan
Attorney Docket Number:	42534-704.313

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16575128

Filing Date: 18-Sep-2019

Applicant/Patent under Reexamination: TALASAZ

Electronic Terminal Disclaimer filed on May 4, 2020

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt	
EFS ID:	39346907
Application Number:	16575128
International Application Number:	
Confirmation Number:	9440
Title of Invention:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION
First Named Inventor/Applicant Name:	AmirAli TALASAZ
Customer Number:	115823
Filer:	Timothy A Hott/Michelle Chan
Filer Authorized By:	Timothy A Hott
Attorney Docket Number:	42534-704.313
Receipt Date:	04-MAY-2020
Filing Date:	18-SEP-2019
Time Stamp:	18:41:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	E202054I41171858
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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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	40958 2d12754d667cdc56f8fd79ac177f8ce70c6aaeba	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30571 9d9bec8159900609a6178062f64e567cae18e909	no	2
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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.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli TALASAZ Serial Number: 16/575,128 Filing Date: September 18, 2019 Title: SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION	Confirmation No.: 9440 Customer No.: 115823 Group Art Unit: 1637 Examiner: Kenneth R. HORLICK

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

AMENDMENT AND RESPONSE TO NON-FINAL OFFICE ACTION

Sir:

This paper is in response to the Office Action mailed on February 14, 2020. This response is being timely filed within the three-month shortened statutory period for reply. Applicant respectfully requests reconsideration of the above-referenced application in view of the following remarks:

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.

AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0001] with the following paragraph:

[0001] This application is a continuation of U.S. Patent Application 16/283,635, filed February 22, 2019 (now U.S. Patent 10,494,678, issued December 3, 2019), which is a continuation of U.S. Patent Application No. 15/872,831, filed January 16, 2018, which is a continuation application of U.S. Patent Application No. 15/828,099, filed November 30, 2017, which is a continuation application of U.S. Patent Application No. 15/467,570, filed March 23, 2017 (now U.S. Patent 9,840,743, issued December 12, 2017), which is a continuation application of U.S. Patent Application No. 14/425,189, filed March 2, 2015 (now U.S. Patent 10,041,127, issued August 7, 2018), which is a national stage entry of international Application No. PCT/US2013/058061, filed September 4, 2013, which claims priority to U.S. Provisional Patent Application No. 61/696,734, filed September 4, 2012, U.S. Provisional Patent Application No. 61/704,400, filed September 21, 2012, and U.S. Provisional Patent Application No. 61/793,997, filed March 15, 2013, and U.S. Provisional Patent Application No. 61/845,987, filed July 13, 2013, each of which is entirely incorporated herein by reference for all purposes.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1. - 30. (Cancelled).

31. (Currently amended): A method for inferring a quantitative measure of microsatellite changes in a sample of cell-free nucleic acid molecules from a subject having a cancer ~~or suspected of having a cancer~~, the method comprising:

(a) ~~non-uniquely~~ tagging a plurality of the cell-free nucleic acid molecules from the sample with molecular barcodes from a set of molecular barcodes to produce ~~a set of~~ tagged parent polynucleotides;

(b) amplifying a plurality of the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;

(c) sequencing a plurality of the amplified tagged progeny polynucleotides to produce a set of sequencing reads;

(d) grouping a plurality of sequencing reads from the set of sequencing reads into families based at least on sequence information of the molecular barcodes, each family having sequencing reads amplified from the same tagged parent polynucleotide;

(e) determining a quantitative measure of sequence reads in ~~each family~~ a plurality of families and a quantitative measure of unique families from among a plurality of families;

(f) inferring a measure of tagged parent polynucleotides in the set of tagged parent polynucleotides based on the quantitative measure of the sequence reads in the plurality of families ~~each family~~ and the quantitative measure of unique families from among the plurality of families;

(g) determining a quantitative measure of microsatellite changes from among a plurality of the families; and

(h) based on the determined quantitative measure of microsatellite changes from among the families, inferring a quantitative measure of microsatellite changes in the number of inferred tagged parent polynucleotides.

32. (Previously presented): The method of claim 31, wherein the sample is a bodily fluid sample selected from the group consisting of blood, plasma, and serum.
33. (Previously presented): The method of claim 31, wherein a molecular barcode from the set of molecular barcodes is attached on both ends of a molecule of the cell-free nucleic acid molecules.
34. (Previously presented): The method of claim 31, wherein the molecular barcodes from the set of molecular barcodes have 2 to 1,000 different molecular barcode sequences.
35. (Currently amended): The method of claim 31, wherein ~~non-unique~~ the tagging comprises performing blunt-end ligation or sticky-end ligation.
36. (Previously presented): The method of claim 31, further comprising selectively enriching the amplified tagged progeny polynucleotides for target regions associated with cancer prior to sequencing.
37. (Previously presented): The method of claim 31, further comprising filtering out sequencing reads that fail to meet a quality threshold.
38. (Previously presented): The method of claim 31, further comprising mapping a plurality of sequencing reads from the set of sequencing reads to a reference sequence.
39. (Currently amended): The method of claim 38, wherein the grouping is based on a combination of sequence information of the molecular barcodes and a beginning base position and an end base position[[s]] of the sequencing reads that map to the reference sequence.
40. (Previously presented): The method of claim 31, further comprising collapsing the sequencing reads in a plurality of families to generate consensus sequence reads.
41. (Previously presented): The method of claim 40, further comprising identifying one or more consensus sequence reads having a somatic mutation as compared to a reference sequence.

42. (Currently amended): The method of claim 31, further comprising determining ~~reporting~~ a treatment regimen for the subject based on the inferred quantitative measure of microsatellite changes in the number of inferred tagged parent polynucleotides.

43. (Currently amended): A method for detecting a genetic variation in one or more microsatellite regions in a sample of cell-free nucleic acid molecules from a subject having a cancer ~~or suspected of having a cancer~~, the method comprising:

(a) ligating molecular barcodes from a set of molecular barcodes having 2 to 1,000,000 different molecular barcode sequences to a population of cell-free nucleic acids obtained from the sample to produce tagged parent polynucleotides;

(b) amplifying the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;

(c) sequencing a plurality of the amplified tagged progeny polynucleotides to produce a set of sequencing reads; and

(d) determining, from among a plurality of [[the]] sequencing reads in the set of sequencing reads, a quantitative measure of polymorphic forms comprising microsatellite changes in the one or more microsatellite regions based at least on sequence information from the molecular barcodes, thereby detecting the genetic variation in the one or more microsatellite regions.

44. (Previously presented): The method of claim 43, wherein the genetic variation in the one or more microsatellite regions comprises an insertion or deletion (indel).

45. (Previously presented): The method of claim 43, wherein the sample is a bodily fluid sample selected from the group consisting of blood, plasma, and serum.

46. (Previously presented): The method of claim 43, wherein a molecular barcode from the set of molecular barcodes is attached on both ends of a molecule of the cell-free nucleic acid molecules.

47. (Previously presented): The method of claim 43, wherein the set of molecular barcodes comprises molecular barcodes having 2 to 1,000 different molecular barcode sequences.

48. (Previously presented): The method of claim 43, wherein the molecular barcodes are ligated to the cell-free nucleic acid molecules by blunt-end ligation or sticky-end ligation.

49. (Previously presented): The method of claim 43, further comprising selectively enriching the amplified tagged progeny polynucleotides for target regions associated with cancer prior to sequencing.
50. (Previously presented): The method of claim 43, further comprising filtering out sequencing reads that fail to meet a quality threshold.
51. (Previously presented): The method of claim 43, further comprising mapping a plurality of sequencing reads from the set of sequencing reads to a reference sequence.
52. (Currently amended): The method of claim 51, further comprising grouping a subset of sequencing reads into ~~a plurality of~~ families based on sequence information of the molecular barcodes and ~~beginning and end base positions of the sequencing reads that map to the reference sequence~~ a start base position of a given sequencing read from among the subset of sequencing reads at which the given sequencing read is determined to start mapping to the reference sequence and/or (2) a stop base position of the given sequencing read at which the given sequencing read is determined to stop mapping to the reference sequence.
53. (Currently amended): The method of claim 52 [[43]], further comprising collapsing the sequencing reads in a plurality of families to generate consensus sequence reads.
54. (Currently amended): The method of claim 53, further comprising identifying one or more consensus sequence reads having the genetic variation as compared to [[a]] the reference sequence.
55. (Previously presented): The method of claim 43, wherein the population of cell-free nucleic acids comprises 1 nanogram (ng) to 100 ng of cell-free nucleic acid molecules.
56. (Previously presented): The method of claim 43, wherein the cell-free nucleic acids are cell-free deoxyribonucleic acid (cfDNA) molecules.
57. (Cancelled).
58. (Previously presented): The method of claim 43, further comprising determining a confidence score based on the presence or absence of the genetic variation detected in the one or more microsatellite regions.
59. (Currently amended): The method of claim 43, further comprising ~~reporting~~ determining a treatment regimen for the subject based on the quantitative measure of polymorphic forms comprising microsatellite changes in the one or more microsatellite regions.

60. (Previously presented): The method of claim 59, further comprising administering the treatment regimen to the subject.

61. (New): A method for detecting a genetic variation in one or more microsatellite regions in a sample of cell-free deoxyribonucleic acid (cfDNA) molecules from a subject having cancer, the method comprising:

(a) tagging a population of cell-free nucleic acids obtained from the sample with molecular barcodes from a set of molecular barcodes to produce tagged parent polynucleotides, wherein the molecular barcodes are attached to both ends of the cfDNA molecules from the population of cfDNA molecules, and wherein a plurality of the tagged parent polynucleotides has identical molecular barcode sequences;

(b) amplifying the tagged parent polynucleotides to produce amplified tagged progeny polynucleotides;

(c) sequencing a plurality of the amplified tagged progeny polynucleotides to produce a set of sequencing reads;

(d) identifying, from among a plurality of sequencing reads in the set of sequencing reads, a plurality of unique sequence reads based at least on sequence information from the molecular barcodes, wherein a unique sequence read corresponds to a nucleic acid sequence of a cfDNA molecule from among the tagged parent polynucleotides; and

(e) determining, from among a plurality of unique sequence reads, a quantitative measure of polymorphic forms comprising microsatellite changes in the one or more microsatellite regions, thereby detecting the genetic variation in the one or more microsatellite regions.

REMARKS

Claims 31-60 were pending prior to entry of the above-referenced claim amendments. Claim 57 is hereby cancelled without disclaimer or prejudice. Claims 31, 35. 39, 42-43, 52-54 and 59 are amended herein better clarify the claimed subject matter and/or correct for antecedent basis or dependency purposes. Claim 61 is newly added. Support the amendments may be found throughout the application as filed. No new subject matter is believed to have been added by these amendments. Therefore, claims 31-56 and 58-61 are pending and set for examination.

I. Specification

In addition to the aforementioned claim amendments, Applicant has amended the specification to reflect the most current priority information of the present application, which corresponds to the information submitted in the Application Data Sheet filed on October 4, 2019.

II. Nonstatutory Double Patenting

A. Claims 31-60 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-30 of US Patent No. 10,494,678 in view of Sacko et al. (US2010/0264331). Claims 31-60 are rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1-33 of US Patent No. 9,902,992 in view of Sacko et al. (US2010/0264331). Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 78, 207-211, 214-222, and 224-226 of copending USSN 15/828,099 in view of Sacko et al. (US2010/0264331). Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 31-33, 35-38, 41-43, and 45-64 of copending USSN 16/575,079 in view of Sacko et al. (US2010/0264331). Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 31-60 of copending USSN 16/593,633 in view of Sacko et al. (US2010/0264331). Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 31-60 of copending USSN 16/593,653 in view of Sacko et al. (US2010/0264331).

Without conceding in the basis of rejection, and solely to expedite the prosecution of this application, Applicant submits herewith terminal disclaimers over the aforementioned patent applications and patents. Accordingly, Applicant respectfully requests that the double patenting rejections be withdrawn.

B. Claims 31-60 are provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 31-48 and 51-60 of copending USSN 16/283,629 in view of Sacko et al. (US2010/0264331). Applicant respectfully submits that the '629 application issued as US Patent No. 10,501,810. Accordingly, the rejection is no longer provisional.

Without conceding in the basis of rejection, and solely to expedite the prosecution of this application, Applicant submits herewith a terminal disclaimer over the aforementioned patent. Accordingly, Applicant respectfully requests that the double patenting rejection be withdrawn.

Applicant respectfully submits that the nonstatutory double patenting rejections to claim 57 are moot in view of the cancellation of the claim.

***

It shall be understood herein that any instance in which Applicant has addressed certain comments set forth by the Office shall not be construed as a concession to other comments or arguments advanced by the Office. Any circumstance in which Applicant has amended or cancelled a claim also does not mean that Applicant concedes to the arguments or positions advanced by the Office with respect to that claim or other claims pending herein.

CONCLUSION

This paper fully addresses the rejections raised in the Office Action mailed February 14, 2020. Applicant believes that the present application is now in condition for allowance. The Commissioner is authorized to charge any underpayment, or credit any overpayment, to Deposit Account No. 60-2231 (Attorney Docket No. GH0002US-CON15).

Respectfully submitted,

GUARDANT HEALTH, INC.

Date: May 4, 2020 By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

GUARDANT HEALTH, INC.
505 Penobscot Drive
Redwood City, CA 94063
Customer No. 115823

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	AmirAli TALASAZ	Confirmation No.:	9440
Serial No.:	16/575,128	Art Unit:	1636
Filing Date:	September 18, 2019	Examiner:	To be assigned
Title:	SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION		

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

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

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-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

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☒ a fee of $240.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

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Respectfully submitted,

Dated: May 4, 2020

By: /Timothy A. Hott/
Timothy A. Hott, Reg. No. 67740

Customer No. 115823
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	1	ADEY, et al. "Rapid, low-input, low-bias construction of shotgun fragment libraries by high-density in vitro transposition" Genome Biology (2010) 11:R119	
	2	Guardant Health, Inc. v. Foundation Medicine, Inc. Civil Action No. 17-1616-LPS-CJB and Guardant Health, Inc. v. Personal Genome Diagnostics Civil Action No. 17-1623-LPS-CJB, Report and Recommendation dated January 7, 2020	
	3	Guardant Health, Inc. v. Foundation Medicine, Inc. Civil Action No. 17-1616-LPS-CJB and Guardant Health, Inc. v. Personal Genome Diagnostics Civil Action No. 17-1623-LPS-CJB, Memorandum Order dated March 23, 2020	

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	4	IPR2019-00634, Patent Owner Response, dated December 4, 2019	
	5	IPR2019-00634, Petitioner's Opposition to Patent Owner's Motion to Amend, dated March 3, 2020	
	6	IPR2019-00634, Petitioner's Reply, dated March 3, 2020	
	7	IPR2019-00652, Patent Owner Response, dated December 4, 2019	
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	9	KAMPS-HUGHES, N. et al. "ERASE-Seq: Leveraging replicate measurements to enhance ultralow frequency variant detection in NGS data"PLOS One (2018)	
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	13	NEWMAN, A. et al. "Integrated digital error suppression for improved detection of circulating tumor DNA" Nature Biotech (2016) 34(5):547-555	
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	15	Office action dated 02/18/2020 for US Application No. 16/601,168.	
	16	Office action dated 03/03/2020 for US Application No. 16/672,267.	
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	18	OU, SHI et al. "Liquid Biopsy to Identify Actionable Genomic Alterations" Am Soc Clin Onc (2018) 978	
	19	SATHIRAPONGSASUTI, J.F. et al. "Exome sequencing-based copy-number variation and loss of heterozygosity detection: ExomeCNV" BioInformatics (2011) 27(19):2648-2654	
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	21	VAN LOO, P. et al. "Allele-specific copy number analysis of tumors" PNAS (2010) 107(39):16910-16915	
	22	WANG, T.T. et al. "High efficiency error suppression for accurate detection of low-frequency variants" NAR (2019) 47 (15):	

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

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Signature	/Timothy A. Hott/	Date (YYYY-MM-DD)	2020-05-04
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Adey et al. Genome Biology 2010, 11:R119
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Rapid, low-input, low-bias construction of shotgun fragment libraries by high-density *in vitro* transposition

Andrew Adey[1†], Hilary G Morrison[2†], Asan[3†], Xu Xun[3†], Jacob O Kitzman[1], Emily H Turner[1], Bethany Stackhouse[1], Alexandra P MacKenzie[1], Nicholas C Caruccio[4], Xiuqing Zhang[3*], Jay Shendure[1*]

Abstract

We characterize and extend a highly efficient method for constructing shotgun fragment libraries in which transposase catalyzes *in vitro* DNA fragmentation and adaptor incorporation simultaneously. We apply this method to sequencing a human genome and find that coverage biases are comparable to those of conventional protocols. We also extend its capabilities by developing protocols for sub-nanogram library construction, exome capture from 50 ng of input DNA, PCR-free and colony PCR library construction, and 96-plex sample indexing.

Background

Massively parallel DNA sequencing methods are rapidly achieving broad adoption by the life sciences research community [1,2]. As the productivity of these platforms continues to grow with hardware and software optimizations, the bottleneck experienced by researchers is increasingly at the front end (the construction of sequencing libraries) and at the back end (data analysis and interpretation) rather than in the sequencing itself.

The input material for commonly used platforms, such as the Illumina Genome Analyzer [3], the Roche (454) Genome Sequencer [4], the Life Technologies SOLiD platform [5], as well as for 'real-time' third-generation sequencers such as Pacific Biosciences [6], consists of complex libraries of genome- or transcriptome-derived DNA fragments flanked by platform-specific adaptors. The standard method for constructing such libraries is entirely *in vitro* and typically includes fragmentation of DNA (mechanical or enzymatic), end-polishing, ligation of adaptor sequences, gel-based size-selection, and PCR amplification (Figure 1a). This core protocol may be preceded by additional steps depending on the specific application, such as cDNA synthesis for RNA-seq libraries [7].

Although generally effective, several aspects of the standard method are throughput-limiting or otherwise suboptimal. These include: (1) Labor: there are several labor-intensive enzymatic manipulations with obligate clean-up steps. (2) Time: the protocol requires 6-10 hours from beginning to end, often including an overnight incubation. (3) Automation: although 96-plex, semi-automated processing has been achieved by large-scale genome centers [8], many researchers lack access to the requisite robotic liquid handling systems and/or instruments for parallelized mechanical fragmentation. (4) Sample indexing: incorporation of barcoded adaptors, which enable concurrent analysis of multiple samples and post-sequencing deconvolution, still requires most steps to be carried out on individual samples prior to pooling [9]. (5) High input requirements: standard protocols for shotgun DNA sequencing suggest 1-10 μg DNA as input material per library. This is often not possible, for example in cancer genomics where sample material can be limited. (6) Coverage bias: biases in sequence coverage correlated with G+C content can arise from steps secondary to library construction, including gel purification [10] and PCR amplification [11]. Amplification-free versions of these protocols may reduce G+C biases and eliminate PCR duplicates [11,12], while potentially increasing input requirements.

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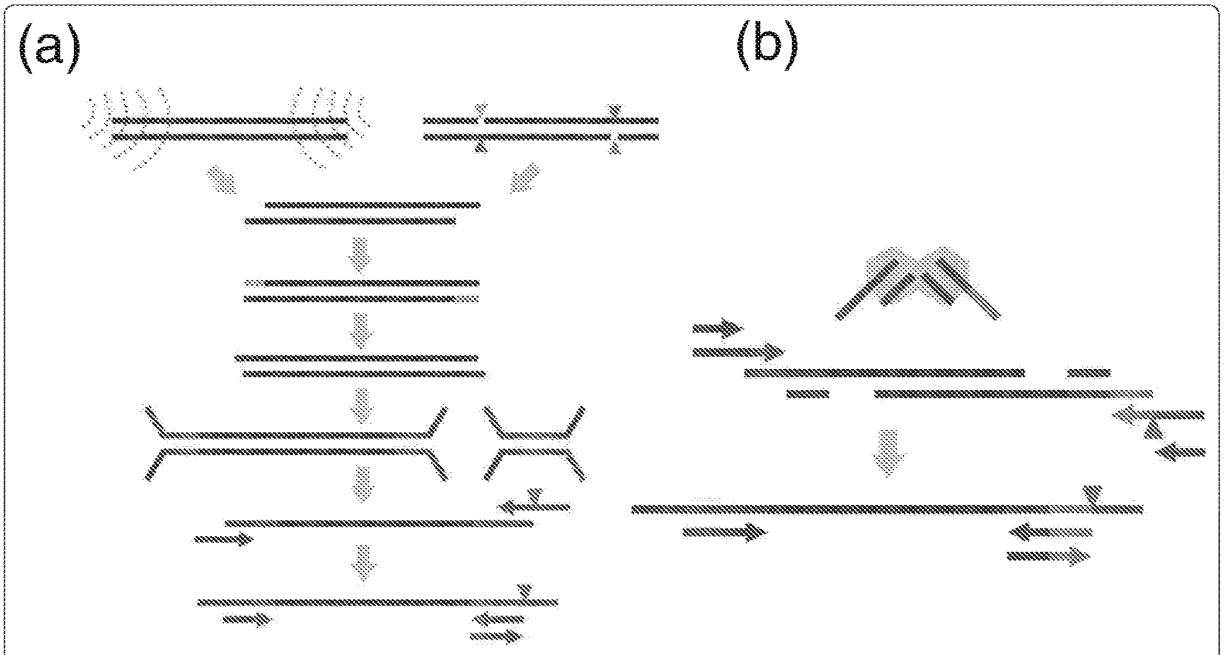


Figure 1 Methods for constructing *in vitro* fragment libraries. **(a)** In the conventional protocol, mechanical or endonuclease fragmentation is followed by end-polishing, A-tailing, adaptor ligation and PCR. **(b)** With transposase-mediated adaptor insertion, fragmentation and adaptor insertion occur in a single 5-min *in vitro* step, followed by PCR. For both methods, a primer-embedded sample-specific barcode can be incorporated during PCR amplification (black triangle). Dark blue: Genomic DNA. Light green: End repaired sequence. Red: A-tail. Magenta/dark green and purple/dark green: Adaptors. Mid blue/brown/orange: Transposase adaptors. Cyan/light green triangles: Endonuclease fragmentation. Grey curved dotted lines: Sonication. Grey hexagon: Transposase.

In the alternative approach that we characterize and extend here, a hyperactive derivative of the Tn5 transposase is used to catalyze *in vitro* integration of synthetic oligonucleotides into target DNA at a high density ('Nextera', Epicentre, Madison, WI, USA). Wild-type Tn5 transposon DNA is flanked by two inverted IS50 elements, each containing two 19 bp sequences required for function (outside end and inside end). A 19 bp hyperactive derivative (mosaic end, ME) is sufficient for transposition provided that the intervening DNA is long enough to allow the two ends to come in close proximity in order to form a complex with a Tn5 transposase homodimer. The relatively low activity of the wild-type Tn5 transposase was cumulatively increased through several classes of mutation [13]. In a classical *in vitro* transposition reaction, hyperactive Tn5 transposomes (hyperactive transposase mutant bound to ME-flanked DNA) bind target DNA and catalyze the insertion of ME-flanked DNA into the target DNA with high frequency [14]. When free synthetic ME adaptors are used instead (isolated from one another, in contrast to ME-flanked DNA in which two ME sequences are linked by the intervening DNA), transposase activity results in fragmentation and end-joining of the synthetic ME adaptor to the 5' end of target DNA. To generate fragment libraries compatible with massively parallel DNA sequencing, limited-cycle PCR is used to append platform-specific primers (Figure 1b).

Significant potential advantages of transposase-catalyzed adaptor insertion as a library preparation method, relative to conventional library preparation, include, firstly, many fewer steps, as the fragmentation, polishing, and ligation steps are replaced by a single 5-minute reaction and optional 10-minute pre-PCR clean-up (Figure 2). Libraries requiring particularly constrained insert size distributions (such as for *de novo* assembly) may optionally be subjected to chip- or gel-based size selection, increasing preparation time by 1 hour or 3-4 hours, respectively. The second advantage is greatly reduced input requirements while maintaining library complexity. This is expected to be possible because of a more efficient conversion of input DNA into sequencing-compatible material. However, these potential advantages are balanced by the competing concern that transposase-mediated fragmentation will introduce significant sequence-dependent biases relative to conventional library construction.

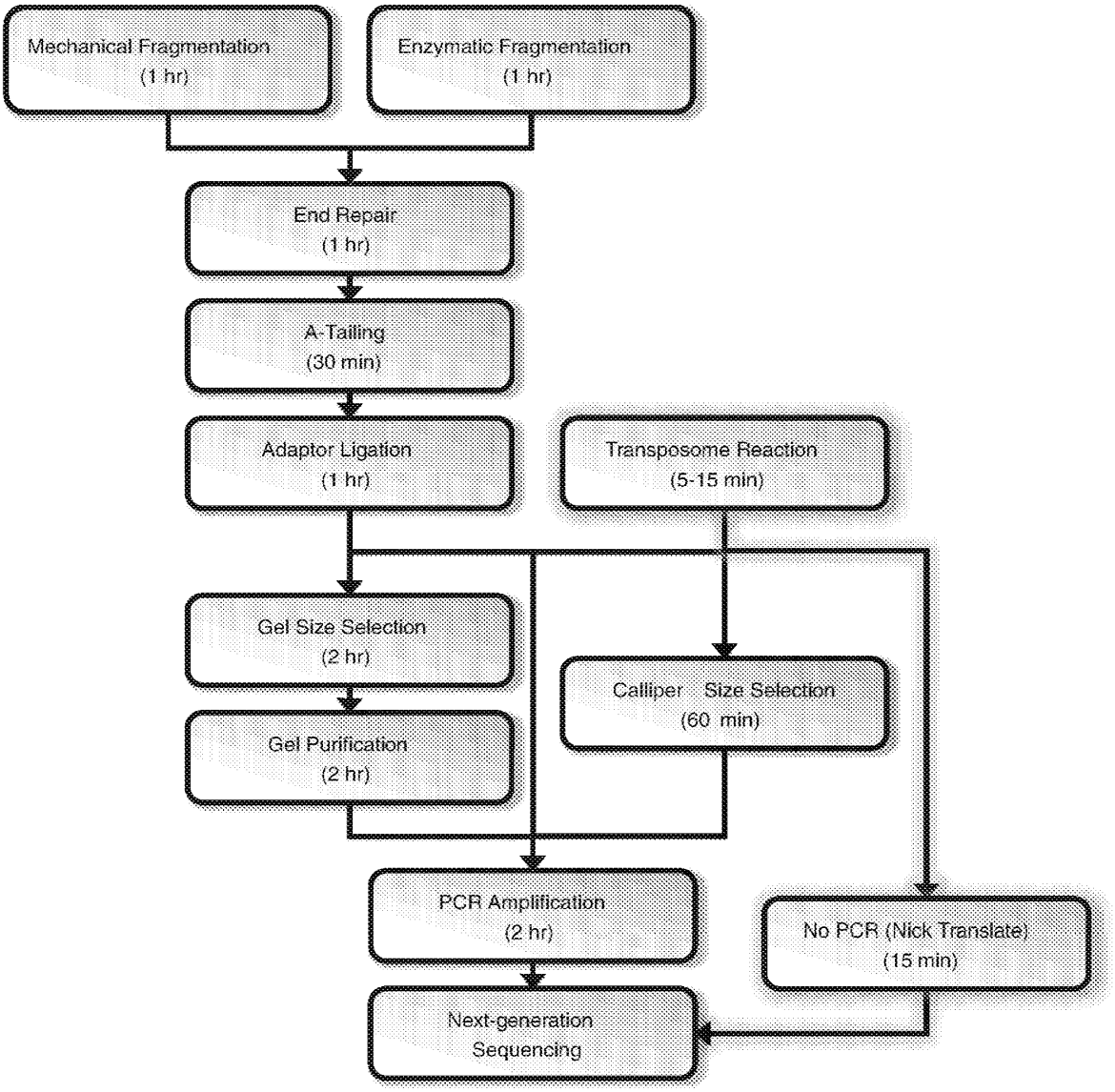


Figure 2 Schematic of steps associated with different library preparation methods. Transposase-catalyzed adaptor insertion significantly reduces the number of steps and time associated with library construction (green path).

Here, we report the results of an extensive comparison of transposase-catalyzed fragmentation with standard library construction protocols. We also describe the development of several derivative protocols for transposase-catalyzed fragmentation that significantly extend its capabilities. To evaluate performance with respect to key parameters including sequence-dependent biases, we compared methods across several organisms and sequencing platforms, including whole genome sequencing of a cell line derived from a previously sequenced human, YH1 [15], on a single flow-cell with the Illumina HiSeq platform. New protocols reported here that extend the utility of this method include: (1) a 96-plex sample indexing scheme, validated on 96 bacterial genomes; (2) capture and sequencing of the complete coding exon content (exome) from 50 ng of input human genomic DNA; (3) a protocol for the construction and sequencing of shotgun libraries from as little as 10 pg of starting material; (4) a PCR-free version of the method that mitigates associated G+C biases and decreases the

total time for library preparation time to less than 30 minutes; and (5) a method analogous to 'colony PCR' for single-step preparation of genomic sequencing libraries directly from bacterial colonies.

Results

Comparison of standard versus transposase-based protocols

We performed a side-by-side comparison of three protocols: (1) standard library construction with mechanical fragmentation; (2) standard library construction with time-dependent endonuclease-based fragmentation ('dsDNA fragmentase', NEB); and (3) transposase-catalyzed adaptor insertion ('Nextera', Epicentre). To evaluate performance on the Illumina platform, sequencing libraries and technical replicates were prepared from two genomic DNA samples (*Homo sapiens* NA18507, *Escherichia coli* CC118) with each of the three methods. Paired-end, 36 bp reads were generated on an Illumina Genome Analyzer IIx (GAIIx). Reads were mapped using BWA [16] to the *E. coli* genome (K12) or human genome (hg18) as appropriate. To evaluate performance on the Roche (454) platform, sequencing libraries were constructed from two bacteriophage DNAs (CRW10 and PA1) with each of the three methods. Libraries were sequenced on a Roche (454) Genome Sequencer FLX, followed by *de novo* assembly (gsAssembler) and read mapping (gsMapper) to the appropriate reference genome. A summary of samples processed and sequence data generated on both platforms is provided in Table S1 in Additional file 1.

Sites of mechanical fragmentation, endonuclease fragmentation, and transposase-catalyzed adaptor insertion were characterized by calculating nucleotide composition in the vicinity of the mapping position of the first base of each sequence read (the fragmentation site; Figure S1 in Additional file 2). This revealed a slight but highly correlated bias for mechanical and endonuclease fragmentation, which suggests that most bias for these two methods is introduced after these protocols converge (for example with A-tailing or adaptor ligation), and that both mechanical fragmentation (here, either acoustic sonication or nebulization) and endonuclease fragmentation (with dsDNA fragmentase) have very low intrinsic biases. In contrast, a more extended signature is observed for sites of transposase-catalyzed adaptor insertion, weakly resembling the reported insertion preference of the native Tn5 transposase (AGNTYWRANCT, where N is any nucleotide, R is A or G, W is A or T, and Y is C or T) [17]. However, when calculated in terms of per-position information content, the bias of transposase-catalyzed adaptor insertion is low, and only slightly greater than the other protocols. For *E. coli* data, maxima of per-position information content over ± 10 bp, on a two-bit scale for fixed positions, are 0.10, 0.11, and 0.16 for mechanical fragmentation, endonuclease fragmentation, and transposase-catalyzed adaptor insertion, respectively. Average information content over ± 10 bp are 0.0056, 0.018, and 0.049, respectively. Equivalently low information contents were observed for human and phage libraries (Table S2 in Additional file 1). The effective bias associated with transposase-catalyzed adaptor insertion is thus greater than with standard library construction, but only modestly so. For *E. coli* and human libraries, signatures of bias were consistent in technical replicates for all three methods.

The greater insertion bias is problematic in a practical sense only if it has a significant impact on the distribution of genomic coverage. Consistent with the low calculated information content of the observed biases, the gross distributions of genomic coverage observed for the three methods are very similar (Figure 3a, b), the exception being the PA1 bacteriophage library, which may be skewed as a result of sequence context in a relatively small genome. Furthermore, similar biases in coverage are observed for different G+C content bins, with reduced representation at both extremes (Figure 3c). As PCR was used to prepare libraries constructed with all three methods, the consistent G+C bias probably arises at that step [11]. We initially predicted that the similar genomic coverage distribution associated with each method was due to factors introduced after the three protocols converge on common steps (solution phase PCR, cluster PCR, and sequencing). However, the correlation in coverage between methods at a per-base level was modest, with transposase-catalyzed adaptor insertion the least correlated with the other methods (Table S3 in Additional file 1).

In this comparative analysis, libraries generated by transposase-catalyzed adaptor insertion were sequenced directly after PCR (without size-selection), and the observed insert size distribution was considerably shorter than the other, size-selected, methods (transposase: 100 ± 47 bp, sonication: 256 ± 48 bp, endonuclease: 244 ± 56 bp; Figure S2 in Additional file 2). To evaluate whether a lower-bound on insert size exists, tails of long-read (101 bp) pairs were aligned to one another and a mapping-independent size distribution constructed, revealing a sharp decrease at about 35 bp that is probably a secondary consequence of steric hindrance of adjacent, attacking transposases (Figure 4). This phenomenon also explains the about 10 bp peaks at the lower end of the insert size distribution resulting from the helical pitch of the DNA as it extends away from the transposase.

With alternative buffer and reaction conditions, other target size ranges can be achieved. For example, the transposon method adapted for Roche (454) library

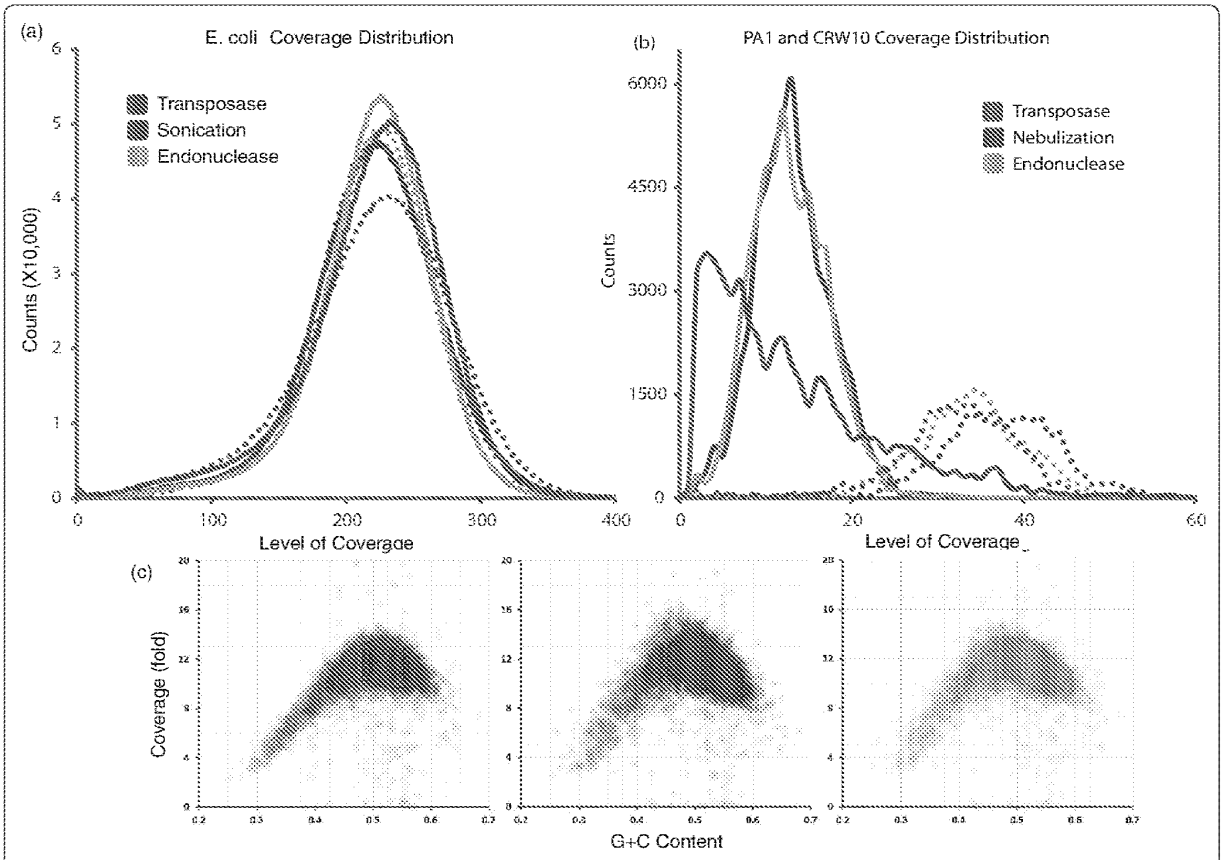


Figure 3 Comparison of coverage bias. (a) Coverage distribution across the *E. coli* genome with transposase (blue), sonication (red), and endonuclease (green) methods (solid lines) and replicates (dotted lines), normalized for total sequencing depth. **(b)** Coverage distribution across the PA1 and CRW10 bacteriophage genomes with transposase (blue), nebulization (red), and endonuclease (green) methods (dotted lines represent replicate libraries). **(c)** G+C bias for *E. coli* was assessed by calculating G+C content of the reference in 500 bp bins and plotting the coverage in each for transposase (blue), sonication (red), and endonuclease (green) methods, all of which show an approximately equivalent bias against the extremes.

construction resulted in significantly longer fragments (300-800 bp; Figure S3 in Additional file 2). To assess whether fragment size of libraries generated by transposase-catalyzed adaptor insertion could be constrained without resorting to gel-based size-selection, we evaluated alternative buffer and reaction conditions in combination with different approaches to post-PCR sample clean-up (Figure S4 in Additional file 2). Notably, an automated chip-based size-selection yielded well-constrained libraries (insert size 162 ± 28 bp).

Whole genome sequencing of human and *Drosophila* genomes

To assess performance further, we conducted whole genome sequencing on transposase-based libraries from *H. sapiens* and *Drosophila melanogaster*. Human genomic DNA from a previously sequenced individual, YH1 [15], was used to generate a series of libraries under different reaction conditions and size-selections that were then subjected to seven lanes of paired-end 90 bp (PE90) sequencing on the Illumina HiSeq platform. Of 934 million reads, 781 million were mapped [16] to the human genome (hg18) for 25× coverage. Although a total of seven libraries were constructed and sequenced to assess reproducibility, the complexity of each individual library was sufficient enough that whole genome sequencing could be carried out using a single library. Variant calling on mapped YH1 data was performed with *samtools* [18] requiring consensus Q30 at called positions (Figure S5 in Additional file 2). By these criteria, 3,556,679 SNPs were called (87% in dbSNP129; transition/transversion ratio (Ti/Tv) = 2.07), substantially greater than the 3,074,097 SNPs reported in initial sequencing of YH1. There were 2,922,525 SNPs shared between the analyses (91% in dbSNP129; Ti/Tv = 2.07), 634,154 SNPs unique to our analysis of this genome (70% in dbSNP129; Ti/Tv = 2.08), and 151,572 SNPs

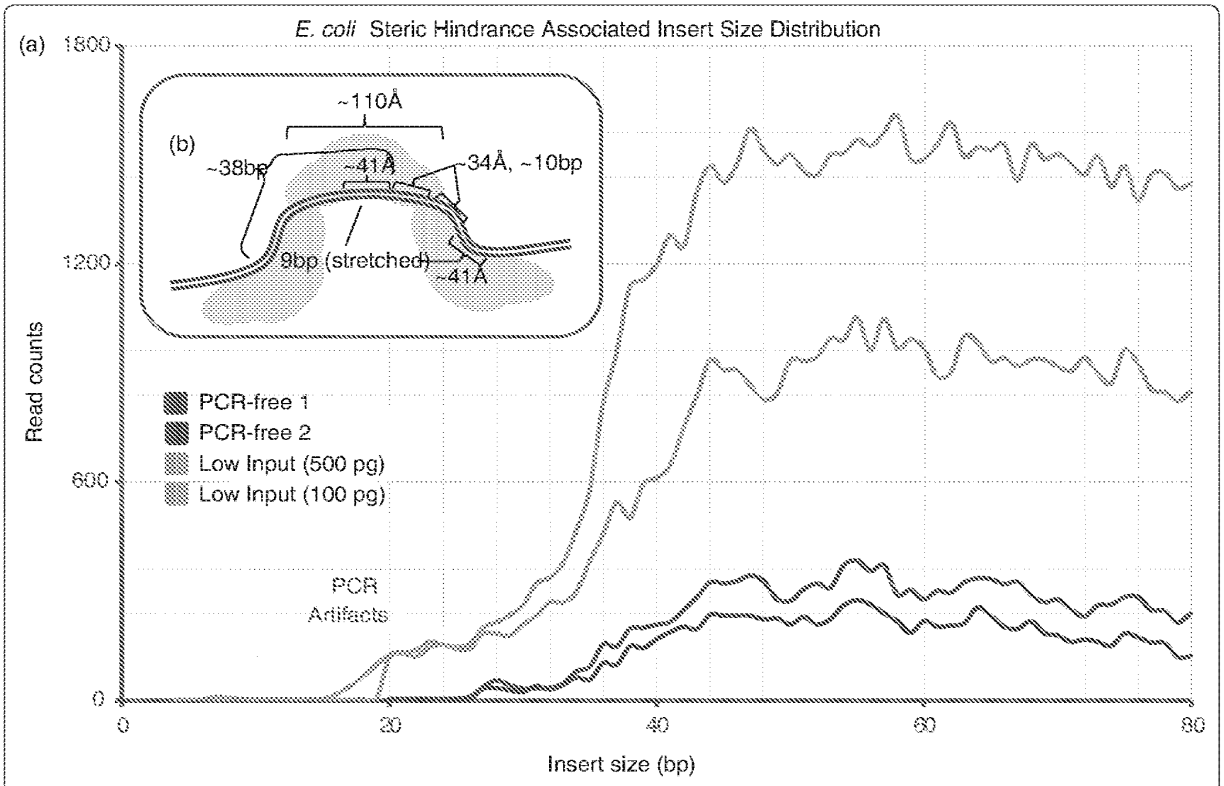


Figure 4 Insert size showing steric hindrance. **(a)** Insert size was generated from libraries spiked into a paired-end 101 bp run resulting in a large proportion of reads reading into the adaptor sequence. Tails of reads were then aligned to one another to discern the insert size between adaptors, resulting in a mapping-independent insert size at the lower extreme. All reads with an insert size less than 25 bp were PCR artifacts. **(b)** The noticeable drop below 40 bp is consistent with a model for complete saturation of transposition events on a given stretch of DNA. The roughly 110 Å transposase homodimer (grey) is bound to genomic DNA (blue), such that the core of the enzyme acts on a 9 bp region drawn out to 41 Å as well as approximately 10 additional bases of DNA flanking either side (~34 Å each) that are essentially protected from a subsequent transposase attack due to steric hindrance. Since the core region is duplicated in the process, the minimum spacing of transposition events is approximately 38 bp.

unique to the initial analysis of this genome (65% in dbSNP129; Ti/Tv = 1.18). The larger number of SNPs identified here may follow in part from greater mappability with longer read-lengths.

In this analysis, cell-line DNA derived from lymphoblasts was used; however, original sequencing of YH1 by Wang *et al.* (2008) [15] was carried out on blood DNA. Notably, 4,036 positions were called as mutations in the cell line and as the reference base in blood, both at a high quality score (30) and in uniquely mappable regions of the genome (see Methods). Of the 1,720 SNPs at a quality over 50 (Ti/Tv = 0.95), a randomly selected 100 were subjected to validation in DNA from blood, DNA from the primary culture used to generate the cell line, and DNA from the cell line. Interestingly, 63 were confirmed as mutations only in the cell line (Ti/Tv = 1.1; one failed assay in primary culture). Of the 37 positions that failed validation, 31 were confirmed as the reference base in blood, primary culture, and cell line (Ti/Tv = 0.48), and the remaining six positions were variant in all three (Ti/Tv = 1.0; one failed assay in primary cell culture). Further experimentation is required to determine whether the validated mutations observed in the cell line represent only mutations occurring during immortalization or propagation of the cell line, or the eventual fixation of somatic mutations present at very low frequencies in primary culture.

Importantly, coverage of YH1's genome in sequencing of libraries derived from transposase-catalyzed fragmentation was relatively uniform when compared with the data generated on this same individual from conventional libraries (Figure 5a). The observed GC bias in whole human genome sequencing data from the two methods was comparable (Figure 5c); however, a modest decrease (23%) in coverage at bins with high GC content (≥60%) was observed with the transposase method. This decrease can potentially be mitigated by a PCR-free version of this

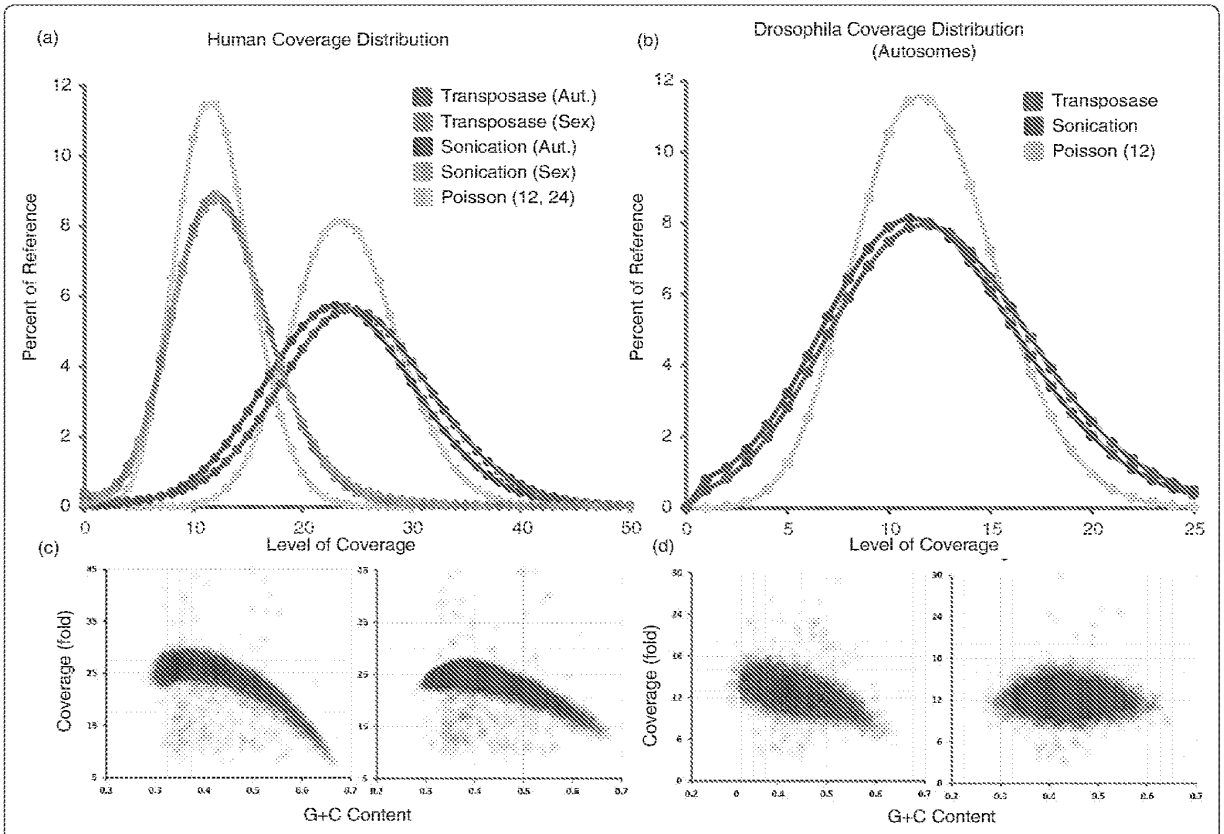


Figure 5 Sequence coverage of human and *Drosophila*. **(a)** Coverage distribution as a percentage of the genome for human (YH1) using transposase (dark blue, autosomes; light blue, sex chromosomes) and sonication [15] (down-sampled to equivalent coverage; red, autosomes; orange, sex chromosomes) methods. Poisson (no bias) distributions (gray) with $\lambda = 12$ (sex chromosomes) and $\lambda = 24$ (autosomes) are also shown. Poisson distribution is the expected if there were absolutely no bias. **(b)** Coverage distribution as a percentage of *Drosophila* autosomes using transposase (blue, down-sampled to equivalent coverage) and sonication (*Drosophila* Population Genomics Project (DPGP), red) methods, as well as Poisson distribution with $\lambda = 12$ (gray). **(c,d)** Coverage with respect to G+C content of the reference in 10 kb or 1 kb bins for (c) human (YH1) and (d) *Drosophila* genomes respectively, for transposase (blue) and sonication (red) methods at comparable global genomic coverage.

method (discussed below), or by alternative PCR conditions (data not shown). For the *Drosophila* genome (dm3), one lane of PE45 sequencing of a transposase-based library on an Illumina GAIIx yielded 16× mean coverage. As with the human genome, the distribution of coverage was largely equivalent to that observed in sequencing *Drosophila* with standard libraries (Figure 5b, d) along with the modest decrease in coverage for regions of high GC content. For both human and *Drosophila* genomes, the signature of bias in the vicinity of insertion sites was similar to that observed in the comparative analysis.

Complexity, that is, the number of molecules of distinct origin, is a critical aspect of shotgun library quality, especially for libraries that will be deeply sampled or subjected to further bottlenecking, such as hybrid capture or size selection. Low complexity manifests as an excess of duplicate reads with identical mapping coordinates, which arise from the same progenitor molecule and can thus skew downstream analyses including SNP calling and genotyping. The complexity of each prepared library here was analyzed by incremental sampling of 50,000 read-pairs without replacement and plotting the number of read-pairs sampled versus the number of unique read-pairs (as determined by mapping location) within the sample. In this analysis, the extent of deviation from linearity provides a measurement of sample complexity. All human genome and *Drosophila* genome libraries sequenced here were found to be highly complex, each comprising over 96% unique read-pairs, even as sequencing depths approached 100 million read-pairs, indicating a single such library could be used for whole genome sequencing (Figure 6). The high complexities achieved are consistent with a high efficiency of conversion of input mass into sequence-

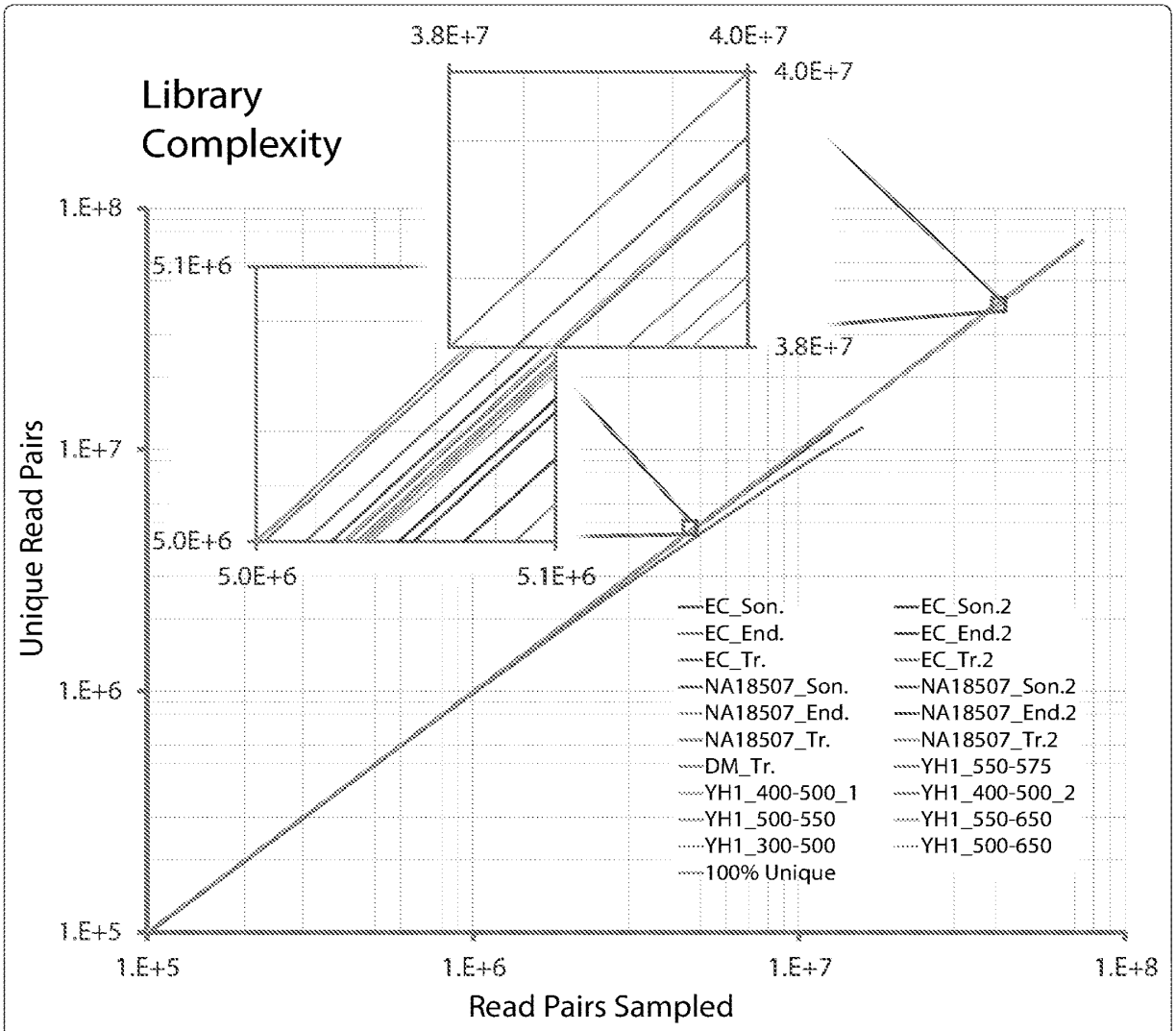


Figure 6 Library complexity. Library complexity for each library shown by incremental, random sampling of 50,000 reads, without replacement, and plotting (on log-log scale) the number of uniquely occurring read-pairs with respect to total number of sampled read-pairs. Species: DM, *Drosophila*; EC, *E. coli*; NA18507 and YH1, human. Methods for fragmentation: End., endonuclease; Son., sonication; Tr., transposase. Size selection ranges are given for the YH1 libraries (all these were generated using transposase. Libararies ending in "2" are replicate libraries. 100% uniqueis in gray, i.e. the distribution if there were no duplicates of any sort.

compatible material as compared with conventional library construction. Less complexity was consistently observed for all *E. coli* libraries, but this is likely to be because we are simply saturating the set of possibilities for start-point pairs that are used to identify PCR duplicates by deep sequencing of a small genome.

Low input targeted sequence capture of the human exome

Exome capture is an increasingly mature technology, but standard protocols require several micrograms of input genomic DNA, which can be problematic when sample is limiting (for example with tumor samples). We subjected a library from 50 ng human genomic DNA by transposome fragmentation to exome capture (Nimblegen SeqCap EZ Exome probes v1.0). Because the adaptor sequences are different from those in libraries prepared using mechanical shearing, custom blocking oligonucleotides were designed and used. After capture, the library was subjected to pre-sequencing real-time PCR with standard primers followed by sequencing on an Illumina GAIIx (SE36). The resulting reads were

aligned to the human genome (hg18) with 78% mapping, of which 47% fell within 100 bp of a targeted exon (Figure S6 in Additional file 2). A direct comparison with an equivalent number of mapped SE36 reads from a standard library, after capture with the same kit, revealed nearly identical complexity for on-target reads (41% and 43% of an equivalent number of on-target SE36 reads with unique start sites for transposome-based and standard libraries, respectively), as well as comparable uniformity (87% and 82% of target bases covered with ≥1 reads for transposome-based and standard libraries, respectively). However, specificity was notably lower (47% of reads on or near target for transposome-based libraries versus 80% for standard libraries). Nonetheless, we note that the standard protocol has been extensively optimized in the context of production-level scaling, and it is likely that specificity in the capture of transposome-based libraries can also be improved upon. Furthermore, the disadvantage of lower specificity is balanced by the advantage of significantly lower input requirements for genomic DNA entering a targeted capture workflow (50 ng for transposase-based libraries versus 3 μg for standard libraries).

Sub-nanogram library construction

To push the limits on library construction using reduced starting material, *E. coli* libraries were generated from 500 pg and 100 pg genomic DNA and sequenced as part of a barcode pool. For each library, expected numbers of read counts were observed (0.5 and 0.6 million mapped reads, respectively) without a noticeable drop in complexity (both libraries over 98% at 0.5 million read-pairs), or coverage uniformity. Next, we generated a library from 10 pg human genomic DNA, or roughly three copies of the human genome, which produced over 2 million uniquely mapped read-pairs. Although complexity was reduced because of the significant decrease in progenitor molecules entering PCR, the potential advantages of sequencing from material approaching a single equivalent of the human genome are substantial.

PCR-free library construction

Standard sequencing libraries for the Illumina platform have been generated without the use of PCR amplification in order to reduce associated biases [11,12]. We developed a similar approach for transposase-based methods by including sequences corresponding to the primers used for cluster formation, i.e. the Illumina adaptor sequences, into the adaptors that are added during the transposition reaction, as opposed to incorporating them during PCR (See Methods). After transposition, a nick translation is performed resulting in Illumina-ready libraries. This method was used to sequence *E. coli* CC118 and human NA18507 with two replicates of each using 100 ng and 200 ng starting material. A noticeable decrease in G+C coverage bias was observed (Figure 7a). Furthermore, complexity for each of these libraries was over 98%. The development of PCR-free, transposase-based library construction reduces the full amount of time required for converting DNA to a sequencing-ready shotgun library to less than 30 minutes.

96-plex sample indexing

Second-generation sequencing platforms suffer from poor granularity. For example, in the data described above, a single PE90 lane on the Illumina HiSeq platform yielded 20 Gb of mappable sequence, which is far in excess of what is required for many projects. Sample indexing (or 'barcoding') is a useful solution, but reported protocols still require most steps of library

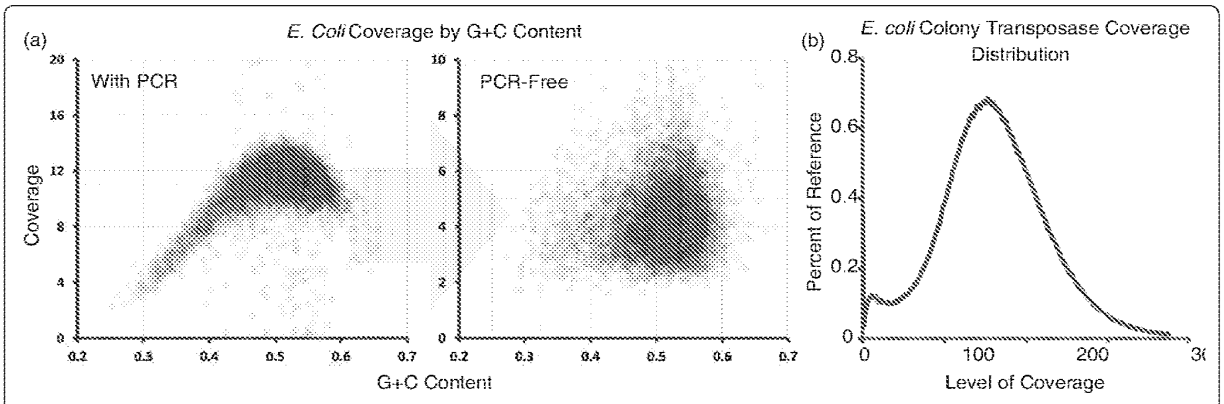


Figure 7 PCR-free reduction in G+C coverage bias and direct-from-colony coverage distribution **(a)** Coverage with respect to G+C content in *E. coli* with and without PCR was assessed by calculating G+C content of the reference in 500 bp bins and plotting the coverage in each for transposase after PCR (left) and with the PCR-free method (right). A significant reduction in coverage bias at the extremes of G+C content is observed. **(b)** Coverage distribution for *E. coli* library prepared directly from cell lysate without purification.

preparation to be carried out on individual samples prior to pooling, and also can suffer from non-uniform performance of individual barcodes [9]. With transposase-catalyzed adaptor insertion, sample indexing could potentially be introduced during adaptor insertion, or during the subsequent PCR step, that is, using a primer-embedded barcode sequence (Figure 1b). To evaluate the compatibility of this method with indexing, we attempted the latter approach. Ninety-six barcodes (9 bp) were designed with a minimal edit distance of four between all pairs and additional constraints on base composition (Table S4 in Additional file 3). Performance was evaluated by subjecting DNA from 96 evolved derivatives of *Pseudomonas aeruginosa* to independent library construction, each with a different barcode-embedded primer during PCR. Post-PCR amplicons were quantified and pooled, followed by several lanes of massively parallel sequencing (PE76, with a third read to collect the 9 bp index). Samples were deconvolved using 9 bp indexes: 92%, 3%, and 3% reads were assigned with 0, 1, and 2 mismatches, respectively, and only 4% could not be unambiguously assigned. With the exception of a few outliers, the distribution of barcode assignments across the 96 was relatively uniform with 90% within a fourfold range (Figure S7 in Additional file 2), as was the proportion of reads mapping to the reference, illustrating the robustness of the library protocol and the indexing scheme.

Constructing genomic libraries directly from bacterial colonies

In evaluating 96-plex sample indexing for 96-plex bacterial genome sequencing with transposase-catalyzed adaptor insertion, the burden of technical effort shifted from library preparation to the isolation of genomic DNA from each isolate. We speculated that integration of the transposase reaction into a 'colony PCR'-like workflow (in which cells from bacterial colonies are directly mixed into a PCR reaction without DNA isolation) could be used to further simplify library preparation for bacterial genome sequencing (Figure S8 in Additional file 2). A pipet tip was used to transfer a small number of cells directly from an *E. coli* colony transformed with pUC19 to a transposase fragmentation reaction (with heat-lysing prior to addition of enzyme). An aliquot of this reaction served as input for PCR amplification without any intervening clean-up step. Sequencing (SE36) yielded 27 million reads, for 170× coverage of the *E. coli* genome (81% of reads) and 37,000× coverage of pUC19 (10% of reads). The remaining 8% mapped to the F plasmid, or an insert cloned into pUC19, or remained unmapped. Coverage of the *E. coli* genome was uniform (Figure 7b). We propose that direct preparation of genomic sequencing libraries from bacterial colonies with no DNA isolation or intervening purification steps will be useful for rapidly preparing sequencing-ready, indexed fragment libraries from large numbers of bacterial isolates.

Discussion

Massively parallel sequencing platforms generally require the conversion of genomic DNA (or other nucleic acid sample) into a fragment library that includes common adaptor sequences that are used to mediate clonal amplification and/or the priming of sequencing reactions. Practical limitations of conventional approaches to generating these libraries include high requirements for labor, time and cost, as well as the low efficiency of mass conversion into sequencing-compatible material. Here, we evaluate an alternative approach in which transposase catalyzes the fragmentation of target DNA and insertion of adaptor sequences in a 5-minute, small-volume reaction. The workflow is thus markedly simpler than the conventional approach yielding significant savings in terms of time and labor (summarized in Figure 2). The input requirements are also over an order of magnitude lower than what is typically used with standard methods, and we demonstrate that high complexity libraries can be generated from as little as 100 pg of input DNA. Furthermore, input can be reduced to as low as just a few copies of the human genome and still produce a significant amount of sequence data. Taking advantage of the simplicity and low input requirements, we developed a method to construct libraries directly from bacterial colonies without DNA isolation or intervening clean-up steps.

Although there are significant advantages, this method nonetheless has its limitations. First, although there is a significant reduction in required steps and time, preparing very large numbers of libraries is still challenging without some degree of automation. Second, one has relatively limited control over the size distribution of fragmentation. In general, the trend is that the insert size distribution is smaller than desired when reacting to completion, and broader than desired when altering reaction conditions to increase the mean insert size. Third, genomes with high G+C contents show greater bias with this method than with conventional methods, although this is potentially correctable in part by the PCR-free approach or through modified PCR conditions. A related point is that we have also observed that performing transposase-catalyzed adaptor insertion on a single PCR product results in significantly greater bias than with shotgun libraries (J. Hiatt, personal communication), potentially secondary to a high molar concentration of a limited number of possible insertion sites. Fourth, we note that this library preparation does not solve an ongoing challenge in the field, which is how

best to efficiently construct high-complexity, long-insert mate-paired libraries.

A comparison of sequence composition in the vicinity of fragmentation sites identified a bias signature that was larger and more extended than that associated with conventional methods. However, we found that this had little impact at the level of coverage for bacterial, human, and *Drosophila* genomes. Nonetheless, the observed impact may be greater in genomes with compositions that correlate with this bias pattern, or in smaller genomes such as bacteriophage. In our view, for most goals, the disadvantage of the slightly greater bias is offset by the large advantages that we observed with respect to speed, simplicity, and low input requirements.

A further reduction in preparation time was achieved in developing a PCR-free, transposase-based library construction method. This approach also decreased biases resulting from amplification, notably in coverage with respect to G+C content. Looking ahead, we anticipate that the partnership of extremely fast, simplified methods for library construction with third-generation 'real-time' sequencing methods may represent a critical path forward in reducing the time between acquiring biological material and obtaining analyzed sequence data to less than 1 hour.

Conclusions

Current methods for preparing *in vitro* DNA fragment libraries for massively parallel sequencing are suboptimal for projects involving limited amounts of starting material or large numbers of samples. Here we have characterized an alternative method of library construction in which highly active transposase catalyzes the simultaneous fragmentation and adaptor ligation in a single 5-minute incubation. Comparison with conventional methods of library preparation, relying on mechanical or endonuclease fragmentation, finds that although transposase-catalyzed adaptor insertion demonstrates a slightly greater insertion bias, this has little impact at the level of genomic coverage and is offset by large advantages with respect to speed, simplicity, and low input requirements.

To fully take advantage of the method and expand on transposase-catalyzed adaptor insertion we applied it on a larger scale, including sequencing a human genome on a single flow-cell of a massively parallel sequencing platform, and validating a 96-plex sample indexing scheme. We also show that transposase-catalyzed adaptor insertion can be integrated with exome sequencing workflows, with the advantage of significantly lower input requirements relative to conventional protocols for targeted sequence capture (50 ng versus several micrograms). In addition, we have generated libraries from as little as 10 pg of starting material and also developed a PCR-free library construction method in order to reduce associated biases and further reduce preparation time to less than 30 minutes. Finally, we demonstrate the direct preparation of genomic sequencing libraries from bacterial colonies with no DNA isolation or intervening purification steps.

Materials and methods

Genomic DNA

Genomic DNA for *H. sapiens* NA18507 (Yoruban) was prepared by the Coriell Institute. *E. coli* CC118 (MC1000 (*araD139* Δ(*ara leu*)*7697* Δ*lacX74 phoAΔ20 galE galK thi rpsE rpoB* $argE_{am}$ *recA1*)) [19], genomic DNA, and CRW10 and PA1 phage genomic DNA were extracted using Qiagen (Valencia, CA, USA) MidiPrep buffers P1, P2, P3 and were cleaned by phenol, purified from low melting point agarose and dissolved in Tris/EDTA (TE) buffer. YH1 genomic DNA was extracted from a lymphoblastoid cell line of Yanhuang [15] using protein K and phenol/chloroform [20] and further subjected to RNase treatment/purification. The *D. melanogaster* genomic DNA was extracted from whole bodies of several individuals by Puregene blood core kit B (Qiagen). The molecular weights of both *Drosophila* and YH1 genomic DNAs were confirmed to be larger than 23 kb by gel electrophoresis (not shown), with no detection of degradation or RNA/protein contamination, and quantified by Quant-iT dsDNA HS assay kit (0.2-100 ng; Invitrogen, Q32854, Carlsbad, CA, USA); of each, an aliquot was diluted to 25 ng/μl for use in library construction. *P. aeruginosa* PAO1 strains were selected for tobramycin resistance at 16 mg/l (41 strains), ciprofloxacin resistance at 4 mg/l (47 strains), or no antibiotic resistance (8 strains). DNA was then isolated using the Wizard® SV 96 genomic DNA purification system (Promega, Madison, WI, USA). Concentrations of isolated DNA were measured using a Nanodrop (Thermo Scientific, Waltham, MA, USA).

Mechanical shearing

Shearing was performed on two 5-μg aliquots of *E. coli* CC118 genomic DNA brought up to 200 μl with TE. Sonication was performed by two 15-min treatments with a Bioruptor sonicator (Wolf Laboratories, Pocklington, UK) at maximum settings in a cold room, switching out the water between treatments to keep samples cool. After sonication, each sample was cleaned up using a QIAquick PCR purification kit, eluting in 30 μl Buffer EB (Qiagen). CRW10 and PA1 phage DNA was fragmented using 5 μg aliquots brought to 100 μl with TE and mixed with 500 μl nebulization buffer (Roche/454, Branford, CT, USA) in a nebulizer cup. Nebulization was carried out using 45 psi (310 kPa) nitrogen for 1 min on ice. The sheared DNA was cleaned and

concentrated using MinElute columns and eluting in Buffer EB (Qiagen).

Enzymatic fragmentation

Enzymatic fragmentation was performed on six 1 μg aliquots of genomic DNA from both *E. coli* CC118 and *H. sapiens* NA18507 added to 2 μl 10× fragmentation reaction buffer, 0.2 μl 100× BSA (NEBiolabs, Ipswich, MA, USA), 2 μl NEB fragmentase enzyme, and nuclease-free water (Ambion, Austin, TX, USA) to 20 μl. Reactions were gently vortexed and spun-down, then incubated on ice for 5 min followed by a time-course incubation at 37°C, removing samples at 15, 20, 30, 45, 60, and 120 min for each of the two sets. Reactions were stopped by placing on ice followed by purification using a QIAquick PCR purification kit, eluting in 30 μl buffer EB (Qiagen). 4 μl of each sample was run on a Novex TBE gel (Invitrogen) to observe size distribution. The 60-min time point showed the desired size range and duplicate samples were prepared by the same method for each organism. Fragmentation of phage DNAs were performed using 1 μg aliquots of PA1 and CRW10 in a 20 μl reaction volume including fragmentation reaction buffer to 1×, BSA, and 2 μl NEB fragmentase enzyme (NEB). The reaction was incubated on ice for 5 min followed by incubation at 37°C for 20 min and stopped with 5 μl 500 mM EDTA and cleaned using MinElute columns (Qiagen).

Post-fragmentation library preparation

Post-fragmentation library preparation on the duplicate samples of *E. coli* CC118 sonication and fragmentase (60 min), and *H. sapiens* NA18507 fragmentase (60 min), was carried out as per standard Illumina methods, including a size selection using Novex TBE gels (Invitrogen), excising the 400-500 bp band. Final PCR amplification was carried out on a Bio-Rad (Hercules, CA, USA) MiniOpticon using SYBR Green I as a dye to monitor amplification. 1 μl of each final library was run on a Novex TBE gel (Invitrogen) for library size confirmation. Nebulized or fragmentase-treated phage samples were size-selected using SPRI beads (Beckman Coulter, Danvers, MA, USA) and used to construct libraries according to standard protocols, including end-polishing, adaptor ligation, fill-in, and single-strand isolation. Adaptor sequences included multiplex identifiers (barcodes).

Transposase-based library preparation

Transposase-based library preparation for *E. coli* CC118 and *H. sapiens* NA18507 Illumina-compatible libraries used 50 ng of genomic DNA brought up to 15 μl in nuclease-free water (Ambion) followed by the addition of 4 μl 5× LMW Nextera reaction buffer and 1 μl Nextera enzyme mix (Illumina-compatible; Epicentre), followed by a gentle vortex and brief centrifugation. Each reaction tube was incubated at 55°C in a thermocycler with a heated lid for 5 min followed by placement on ice and immediate purification using a QIAquick PCR purification kit and elution in 20 μl buffer EB (Qiagen). Suppression PCR was then carried out using 10 μl of the eluate as template with 11.5 μl nuclease-free water (Ambion), 25 μl 2× Nextera PCR buffer, 0.5 μl SYBR Green, 1 μl 50× Nextera primer cocktail (Illumina-compatible), 1 μl 50× Nextera adaptor 2 (barcodes 1-2 for *E. coli* and 3-4 for *H. sapiens*), and 1 μl Nextera PCR enzyme. The reaction was cycled in a Bio-Rad MiniOpticon to monitor the reaction under the following conditions: (1×) 3:00 min at 72°C and (1×) 0:30 min at 95°C, followed by 13 cycles of [0:10 min at 95°C, 0:30 min at 62°C, 3:00 min at 72°C] for *E. coli* barcodes 1 and 2 and *H. sapiens* barcodes 3 and 4 (12 cycles for *H. sapiens* barcode 4). 1 μl of each post-PCR library was electrophoresed through a Novex TBE gel (Invitrogen) for library size confirmation. Size selection of the *E. coli* CC118 transposase libraries was carried out at Epicentre Biotechnology using Agencourt AMPure (> 300 bp size selection), Zymo DNA purification (no size selection), or Caliper (350 ± 10% bp size selection) methods. The *D. melanogaster* library was constructed by pooling two standard Nextera reactions following the manufacturer's protocol (Epicentre). For each reaction, 50 ng genomic DNA was initially tagmented (*in vitro* transposase-catalyzed adaptor insertion) at 55°C for 5 min, and then MinElute purified. This was followed by PCR amplification with same conditions as with *H. sapiens* and *E. coli* libraries for 12 cycles. 400-450 bp gel-based size selection was carried out prior to sequencing.

A total of seven *H. sapiens* YH1 libraries were constructed, differing in mass of DNA, number of PCR cycles, and selected DNA fragment size. These included two (about 500 bp and about 550 bp) produced from pooling five standard Nextera reactions, three (400-500 bp, 500-550 bp and 550-600 bp) produced from pooling two modified reactions with nine cycles of PCR enrichment, and another two libraries (300-500 bp and 500-650 bp) from a single tagmentation reaction using 500 ng starting DNA with five cycles of PCR enrichment. The insert-size distribution and final yields for the *Drosophila* and *H. sapiens* YH1 libraries were validated separately using a 2100 Bioanalyzer (DNA 1000 and 7500 kit; Agilent, Santa Clara, CA, USA) and quantitative PCR.

P. aeruginosa PAO1 Illumina-compatible shotgun libraries were prepared for each strain using Epicentre Biotechnologies' Nextera DNA sample preparation kits with a customized, unique 9 bp barcode sequence for each strain. The tagmentation reaction consisted of

200 ng PAO1 DNA, 25 μl Nextera high molecular weight buffer, 1 μl Nextera transposase enzyme, and water to a total volume of 20 μl. The reaction was incubated for 5 min at 55°C, cleaned using Qiagen MiniElute columns, and eluted in 11 μl water. PCR reactions included 5 μl of the fragmented DNA, 17 μl water, 25 μl Nextera PCR buffer, 1 μl Nextera PCR enzyme, 1 μl of a Nextera primer cocktail containing two short primers (at 10 μM each) and one long Illumina-compatible adaptor (at 5 μM), and 1 μl of the barcode containing Illumina adaptor (at 5 μM). PCR conditions used were the same as above using 12 cycles of amplification, followed by MinElute clean-up as before. Samples were run on a Novex TBE polyacrylamide gel to confirm library quality, and DNA concentrations measured using a Nanodrop.

For the Roche (454)-compatible libraries, standard Nextera reaction conditions were used with 50 ng CRW10 (barcode 11) or PA1 (barcode 10) bacteriophage DNA, 454-Titanium compatible kit components and standard PCR methods, cycling 15 times. The PCR products were purified using Qiagen MinElute columns. Library fragment sizes were assessed using an Agilent Bioanalyzer DNA1000 chip.

Targeted sequence capture of the human exome

Libraries were prepared by transposase-catalyzed adaptor insertion by previously described methods using 50 ng genomic DNA (BK229.03, SFARI-SSC), 1 μl transposomes, 4 μl 5× HMW buffer, and water to 20 μl. Samples were incubated at 55°C for 5 min then cleaned up (AMPure) and eluted in 20 μl followed by the addition of 25 μl 2× Nextera PCR buffer, 1 μl 50× Nextera primer cocktail, 1 μl Nextera PCR enzyme, 0.5 μl 100× SYBR Green, and 1 μl of a barcoded adaptor (Table S4 in Additional file 3) with water to 50 μl. Reactions were carried out on a Bio-Rad MiniOpticon using recommended cycling conditions for 12 rounds. Each tube was cleaned up (AMPure, Agencourt, Boston, MA, USA) and checked for size and quantity on an Agilent Bioanalyzer DNA 1000 chip. One sample was selected for capture using all of the 414.6 ng for hybridization to Nimblegen (Madison, WI, USA) SeqCap EZ Exome probes v1.0 as per Nimblegen protocols using custom blockers (Nextera_Block1: 5'-AAT GAT ACG GCG ACC ACC GAG ATC TAC ACG CCT CCC TCG CGC CAT CAG AGA TGT GTA TAA GAG ACA G-3', Nextera_Block1_REV: 5'-CTG TCT CTT ATA CAC ATC TCT GAT GGC GCG AGG GAG GCG TGT AGA TCT CGG TGG TCG CCG TAT CAT T-3', Nextera_Block2: 5'-CAA GCA GAA GAC GGC ATA CGA GAT CGG TCT GCC TTG CCA GCC CGC TCA GAG ATG TGT ATA AGA GAC AG-3', Nextera_Block2_REV: 5'-CTG TCT CTT ATA CAC ATC TCT GAG CGG GCT GGC AAG GCA GAC CGA TCT CGT ATG CCG TCT TCT GCT TG-3') for 72 h at 47°C. After hybridization, wash was performed as per Nimblegen protocols with streptavidin-coupled magnetic beads. Finally, PCR amplification was performed on exome captured library (Post_Cap_Short_For_Amp: 5'-AAT GAT ACG GCG ACC ACC GAG ATC T-3', Post_Cap_Short_Rev_Amp: 5'-CAA GCA GAA GAC GGC ATA CGA GAT-3'; 1× [0:30 min at 98°C], 17× [0:10 min at 98°C, 0:30 min at 65°C, 0:45 min at 72°C]) followed by clean up (AMPure) and sequencing on an Illumina GAIIx SE36 run.

PCR-free library preparation

Adaptor sequences (NoPCR1: 5'-AAT GAT ACG GCG ACC ACC GAG ATC TAC ACG CCT CCC TCG CGC CAT CAG AGA TGT GTA TAA GAG ACA G-3', and NoPCR2: 5'-CAA GCA GAA GAC GGC ATA CGA GAT CGG TCT GCC TTG CCA GCC CGC TCA GAG ATG TGT ATA AGA GAC AG-3') were designed to contain the original 'Nextera' adaptor sequences, but with an additional 5' overhang of either P1 or P2 on adaptor 1 or adaptor 2, respectively (i.e. sequences to make compatible with cluster PCR on Illumina flowcell), thus eliminating the need to add them during a PCR step. The 5' phosphorylated reverse compliment of the 19 bp mosaic end (ME: 5'-Phos-CTG TCT CTT ATA CAC ATC T-3') sequence was hybridized to NoPCR1/2 by combining 5 μl of each NoPCR1 and NoPCR2 with 10 μl ME reverse complement all at 100 μM with 80 μl TE, followed by denaturation at 95°C for 5 min then slow cooling to room temperature for a final annealed adaptor concentration of 10 μM. Transposomes were assembled by incubating 5 μl annealed adaptors at 10 μM with 5 μl 100% glycerol and 10 μl Ez-Tn5 transposase (Epicentre) and allowed to incubate at room temperature for 20 min.

Tagmentation was carried out using previously prepared *E. coli* (CC118) or human (NA18507) genomic DNA using either 100 or 200 ng of DNA, 5 μl prepared transposomes, 2 μl 5× Nextera HMW buffer (Epicentre), and water to 10 μl. Reactions were incubated at 55°C for 5 min, followed by the addition of 25 μl 2× FailSafe PCR master mix (Epicentre), 1 μl FailSafe DNA polymerase (Epicentre), and 14 μl nuclease-free water (Ambion), and subsequent 5 min incubation at 72°C for nick translation. Tubes were then cleaned up using Qiaquick MinElute PCR purification columns (Qiagen), eluting in 12 μl buffer EB.

For each reaction, 2 μl was used as template for a real time PCR on a MiniOpticon (Bio-Rad) using 0.5 μl SYBR Green, 25 μl 2× Nextera PCR master mix, 1 μl Nextera PCR enzyme and nuclease-free water to 50 μl. Alongside the NoPCR reactions, libraries of known concentrations were used as template at successive dilutions

to be used as a standard for rough library quantification. Standard Nextera cycling conditions were used, without the initial 72°C extension step. PCR reactions were cleaned up by Qiaquick PCR purification columns and run on a Noved 6% TBE PAGE gel (Invitrogen) for library size verification. After quantification, libraries were sequenced as per standard Illumina GAIIx protocol as a paired-end 36 bp run.

Low input transposase-based library preparation

For the 500 pg and 100 pg *E. coli* (CC118) libraries and 10 pg human library (NA18507, Coriell), genomic DNA (in 1 μl volume) was incubated with 1 μl Nextera Illumina-compatible transposomes (Epicentre) at a 1 to 50 dilution (1 μl Nextera enzyme, 24 μl TE, 25 μl 100% glycerol), 1 μl 5× Nextera HMW buffer, and 2 μl nuclease-free water (Ambion). To avoid contamination, all dilutions and reaction preparation was carried out in a PCR hood. Reactions were incubated at 55°C for 5 min followed by addition of 25 μl 2× Nextera PCR buffer, 0.5 μl SYBR Green, 1 μl 50× Nextera primer cocktail, and 1 μl 0.5 μM barcode adaptor 2 (barcodes A6, A9, or A4 for 500 pg and 100 pg *E. coli* DNA, or 10 pg human DNA, respectively) and cycled under standard Nextera conditions in a MiniOpticon (Bio-Rad) real-time PCR thermocycler. Both reactions were removed after 20 cycles and cleaned up using Qiaquick MinElute columns, eluting in 20 μl EB. Libraries were run on a 6% Novex TBE PAGE gel (Invitrogen) for size verification and sequenced as barcoded spike-ins as per standard Illumina GAIIx protocol as a paired-end 101 bp (plus 9 bp barcode) run for *E. coli* libraries and a paired-end 36 bp (plus 9 bp barcode) run for human.

Direct colony-based library preparation

Fusion-Blue chemically competent *E. coli* (Clontech, Mountain View, CA, USA) were transformed with pUC19 bearing a 2 kbp insert of human genomic DNA, and then plated on Luria broth (LB) + ampicillin. A small number of cells were picked from a single bacterial colony with a 10 μl pipette tip, and then transferred with dipping into 15 μl nuclease-free H_2O. The suspended cells were heat-lysed at 95°C for 5 min, then placed on ice for 2 min. Nextera 5× LMW reaction buffer and enzyme (Illumina-compatible; Epicentre) were added to the sample, followed by brief mixing and incubation at 55°C for 5 min. The reaction was then stopped by heating to 70°C for 15 min. Sequencing-compatible primer sites were added in a 50 μl PCR reaction using 5 μl of the transposase reaction directly as template without intervening purification. PCR was carried out with 31.6 μl H_2O, 10 μl Kapa 2G robust A buffer 5× (Kapa Biosystems, Cape Town, South Africa), 1 μl dNTP mix (10 mM each), 0.25 μl SYBR Green 100×, 1 μl 50× Nextera primer cocktail, 1 μl 50× Nextera adaptor 2, and 0.20 μl Kapa 2G robust polymerase; cycling conditions were as described by Epicentre. The amplification reaction was cleaned up with a Qiaquick PCR clean-up column (Qiagen) and eluted into 50 μl EB.

Sequencing

Sequencing of the *H. sapiens* NA18507, *E. coli* CC118, and *D. melanogaster* libraries was done on an Illumina Genome Analyzer IIx as paired-end 36, 36, and 45 bp runs, respectively, using standard read primers for sonication and fragmentase libraries, run in individual lanes, and Nextera read primers for Nextera libraries. *H. sapiens* YH1 libraries were run on an Illumina HiSeq2000 as paired-end 90 bp run using Nextera read primers. Phage libraries contained library-specific barcodes and were run as multiplexed samples using GS FLX Titanium sequencing protocols. *P. aeruginosa* libraries were pooled by combining 100 ng of each strain library, and sequenced on an Illumina Genome Analyzer IIx with a paired-end 76-cycle run.

Short read mapping

Short read mapping was done on the *E. coli* CC118, *D. melanogaster* and *H. sapiens* (NA18507 & YH1) Illumina GAIIx or HiSeq2000 sequenced samples by converting the raw sequence files to fastq format and then mapping to the hg18 (NCBI36) reference using the BWA [16] alignment software. After mapping, PCR duplicates were removed, as well as read-pairs with an insert size shorter than that of the read length.

Long read assembly

Long read assembly from bacteriophage samples sequenced on the Roche GS FLX Ti was done using Roche's newbler assembler under default parameters. Individual reads from each dataset were mapped against the assembled genome using gsMapper (Roche Software Release: 2.3 (091027_1459)).

Fragmentation site characterization

Fragmentation site characterization was carried out by stacking all regions of the genome flanking forward strand mapping start locations and the reverse complement of reverse strand start locations followed by calculating nucleotide frequencies at each position relative to the fragmentation site, thus generating a positional weight matrix (PWM). The PWMs then were imported into the SeqLogo (Oliver Bembom, Dept. of Biostatistics, University of California, Berkeley, 2008) package for Bioconductor in R and used to generate positional

information content (IC) and sequence logos using the equation outlined by T. D. Schneider *et al.* [21,22]:

$$IC(w) = \log_2(J) + \Sigma_{j=1}^{J} p_{wj} \log_2(p_{wj}) = \log_2(J) - entropy(w)$$

where J is the number of variables in the alphabet (4; A, C, G, or T), and j is the base at position w. This equation does not factor in the background nucleotide frequencies.

Normalization of Illumina GAIIx coverage

Normalization of Illumina GAIIx coverage for the *E. coli* (non-size-selected) data was done by dividing the coverage at each position in the genome by the total number of mapped bases and then multiplying by a constant (the average number of mapped bases was close to 1 Gb, therefore 10^9 was used as the constant).

Coverage distribution histograms

Coverage distribution histograms were generated by calculating the number of times each base of the genome was sequenced and plotting the frequency of each level of coverage.

Coverage by G+C content

Coverage by G+C content plots were generated by binning the reference genome into 500 bp bins for *E. coli*, 10 kbp bins for human, and 1 kbp bins for *Drosophila* (other sizes were also investigated, resulting in very similar distributions) and calculating the G+C content of each bin, followed by plotting the coverage of that bin.

Library complexity

Library complexity was calculated by random sampling of 50,000 read-pairs without replacement and plotting the number of uniquely occurring read-pairs versus the total number of sampled read-pairs.

Insertion size distributions

Insertion size distributions were generated by taking the distance between the start mapping location of the first read and the end mapping location of the second read for every read-pair and plotting the frequency of occurrences of each insert size.

SNP calls

SNP calls for the YH1 genome were generated using the SAMtools [18] variant caller with a maximum coverage of 1,000 and minimum quality score of 30. Prior to variant calling, read-pairs with an insert size less than 90 bp and reads not properly paired were removed to reduce noise. Calls were then compared with the SNPs reported by Wang *et al.* (2008) [15] and to dbSNP build 129.

Cell-line-discordant SNP calls

In order to minimize false calls due to mapping errors, a repeat-masked version of hg18 was used along with further masking with respect to mappability according to the UCSC Genome Browser 'Rosetta 35mer uniqueness' and excluding all regions with a score of 0 (this score means that the sequence maps perfectly to multiple locations in the genome). This track was used because it was generated using the BWA aligner that was used in our analysis, and because the original YH1 sequence data is made up of 36 bp reads. Out of this newly masked genome, positions were called that had a SNP quality score in the cell line over 30, a reference call in blood over 30, and coverage less than 100× in both datasets. Of those with a quality score of 50 in both for their calls, 100 were randomly chosen for validation.

Validation was carried out using a mass spectrometry assay (Sequenom, San Diego, CA, USA). Primers for PCR amplification and extension were successfully designed for 100 mutation sites using the Sequenom MassArray Assay Design v3.1. PCR amplification, shrimp alkaline phosphatase treatment of unincorporated dNTPs, probe extension and resin desalting were carried out in sequence using the conditions described elsewhere [23]. Sequenom genotyping was performed in parallel for genomic DNA from YH1 blood and the same batch of lymphoblastoid cell lines as was used for sequencing. A negative control and technical replicate were also run in parallel for each typed position. Genotyping of all 100 testing sites passed the filter criteria of: (1) no failing extension, (2) no false positive in the negative control, (3) consistency between two technical replicates. Genotyping was further performed for the 100 positions in the YH primary lymphoblastoid cell lines using the same method, with 98 meeting the above filter criteria.

Exome analysis

Sequence reads from transposase-based libraries subjected to human exome capture were aligned to the human reference (hg18) using BWA [16]. Each aligned base was deemed to be on target if it was within 100 bases of a targeted sequence. At each position within target regions, coverage was assessed and any position with a depth of at least one was considered covered. Comparison to standard exome methods was made by trimming read 1 of a PE76 lane from a GAIIx down to 36 bases and aligning it the same way. Because the standard library had fewer reads mapped, 28 million reads were randomly taken from both libraries and above analysis performed. Complexity was interrogated by taking an equivalent number of on-target SE36 reads generated

by each method and calculating the percentage with unique start-points.

Barcode design

Barcode design yielded a set of 96 × 9 bp sequences in which each 9 bp sequence contained no homopolymer run of three or more bases, had a GC content of ≤ 60%, was a edit distance of at least four away from all other members of the set of 96, and screened negative when compared with other adaptor and primer sequences used here. Also, we took care to ensure that each base (A, G, C, or T) was represented at least once in each 9 bp barcode, and at least once in each position along the 9 bp.

Barcode deconvolution

Barcode deconvolution for pooled, multiplexed *Pseudomonas* samples was carried out by computing the Levenshtein edit distance between the obtained index read and each of the 96 barcode sequences used. The corresponding read-pair was assigned to a barcode when that barcode was within edit distance of 2 of the index read, with the next closest matching barcode being at least two further edits away.

Data accessibility

All sequence data described here is being deposited in the NCBI Sequence Read Archive (SRA) under accession SRP004087.

Additional material

Additional file 1: Supplementary Tables 1-3.

Additional file 2: Supplementary Figures 1-8.

Additional file 3: Supplementary Table 4. S4: barcode adaptors.

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Authors' contributions

AA, HGM, Asan, XX, NCC, XZ, and JS conceived the study and planned experiments. AA analyzed all data, conducted comparison experiments with the Illumina platform, and developed the PCR-free protocol, the exome capture protocol, and the low-input protocol. HGM conducted comparison experiments and accompanying analyses with the 454 platform. Asan, XX, and XZ performed YH1 and *Drosophila* genome sequencing, and SNP validation. JOK developed the direct-from-colony library construction protocol and analyzed the resulting data. APM performed exome capture experiments. EHT, BS and AA developed and tested the 96-plex barcoding protocol. AA and JS wrote the manuscript. All authors reviewed drafts, contributed comments, and approved the final manuscript.

Competing interests

NCC is an employee of Epicentre Biotechnologies. The other authors declare that they have no completing interests.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GUARDANT HEALTH, INC., Plaintiff, v. FOUNDATION MEDICINE, INC., Defendant.	Civil Action No. 17-1616-LPS-CJB
GUARDANT HEALTH, INC., Plaintiff, v. PERSONAL GENOME DIAGNOSTICS, INC., Defendant.	Civil Action No. 17-1623-LPS-CJB

REPORT AND RECOMMENDATION

In these two related actions filed by Plaintiff Guardant Health, Inc. ("Guardant" or "Plaintiff") against Defendants Foundation Medicine, Inc. ("FMI") and Personal Genome Diagnostics, Inc. ("PGDx" and collectively with FMI, "Defendants"), Guardant alleges infringement of United States Patent Nos. 9,598,731 ("the '731 patent"), 9,834,822 ("the '822 patent"), 9,840,743 ("the '743 patent") and 9,902,992 ("the '992 patent" and collectively with the other patents, "the asserted patents" or "the patents-in-suit"). Presently before the Court are two motions filed by Plaintiff pursuant to Federal Rule of Civil Procedure 12(b)(6) seeking an order dismissing Defendants' counterclaims of unenforceability of the '992 patent due to inequitable conduct (the "Motions"). (Civil Action No. 17-1623-LPS-CJB, D.I. 285; Civil Action No. 17-1616-LPS-CJB, D.I. 169) For the reasons that follow, the Court recommends that the Motions be DENIED.

I. BACKGROUND

The Court hereby incorporates by reference the summary of the background of this matter set out in its September 6, 2019 Report and Recommendation. (Civil Action No. 17-1623-LPS-CJB, D.I. 354 at 2-3) Below, it will include additional factual background relevant to the instant Motions.

In June 2019, both Defendants filed Answers and Counterclaims with regard to the operative Third Amended Complaint; among the counterclaims included in both of these pleadings were four counterclaims seeking a declaratory judgment of unenforceability for inequitable conduct of each of the four patents-in-suit. (Civil Action No. 17-1623-LPS-CJB, D.I. 284 at 12-29, 46-48 (filed June 13, 2019); Civil Action No. 17-1616-LPS-CJB, D.I. 168 at 12-40 (filed June 20, 2019)).[1] PGDx's counterclaims regarding inequitable conduct are generally very

[1] FMI had previously an Answer and Counterclaims in response to Plaintiff's Second Amended Complaint on May 7, 2019. (Civil Action No. 17-1616-LPS-CJB, D.I. 148) On the same day, May 7, 2019, Plaintiff filed its now-operative Third Amended Complaint. (Civil Action No. 17-1616-LPS-CJB, D.I. 149) On June 20, 2019, Plaintiff filed its instant Motion to dismiss FMI's inequitable conduct counterclaim as to the '992 patent, which was directed to the counterclaim found in the then-operative Answer and Counterclaims to Plaintiff's Second Amended Complaint. (Civil Action No. 17-1616-LPS-CJB, D.I. 169) But on that same date, June 20, 2019, FMI filed its Answer and Counterclaims to the Third Amended Complaint; that pleading simply re-alleged the inequitable conduct counterclaims that had previously been set out in FMI's May 7, 2019 pleading. (Civil Action No. 17-1616-LPS-CJB, D.I. 179 at 1 n.1 (FMI confirming that the subsequently-filed counterclaims simply "re-alleg[ed] the inequitable conduct allegations"); *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 148)) This is all to say that although Plaintiff's instant Motion here was technically directed to the FMI counterclaim found in FMI's May 7, 2019 pleading, the Court assumes that Plaintiff's arguments apply in the just the same way to that same counterclaim found in FMI's now-operative June 20, 2019 pleading.

A similar thing happened in the PGDx matter. (*See* Civil Action No. 17-1623-LPS-CJB, D.I. 308 at 2 n.1) As with the FMI matter, there appears to be no dispute in the PGDx matter that Plaintiff's arguments regarding PGDx's inequitable conduct counterclaim apply to the counterclaim found in PGDx's now-operative Answer and Counterclaims to Plaintiff's operative Third Amended Complaint. (*Id.* ("PGDx interpreted the Motion as challenging the updated

similar to FMI's inequitable conduct counterclaims, though (as the Court will set out further below) the respective allegations are not identical. (*Id.*) Both sets of counterclaims allege misconduct involving Guardant's co-founder Dr. Helmy Eltoukhy. More specifically, Defendants allege that: (1) while he was still employed by his former employer (Illumina, Inc., or "Illumina"), Dr. Eltoukhy helped conceive of the purported inventions claimed in the four patents-in-suit; and (2) despite this, Dr. Eltoukhy was wrongfully omitted from the list of inventors on the applications for three of those four patents (i.e., all but the application leading to the '992 patent). (*Id.*)[2]

In response, Plaintiff filed the instant Motions, seeking to dismiss Defendants' inequitable conduct counterclaims regarding the '992 patent (that is, FMI's Twelfth Counterclaim and Count XII of PGDx's counterclaims). (Civil Action No. 17-1623-LPS-CJB, D.I. 285 (filed June 13, 2019); Civil Action No. 17-1616-LPS-CJB, D.I. 169 (filed June 20, 2019)) Briefing on the Motions was completed by July 19, 2019. (Civil Action No. 17-1616-LPS-CJB, D.I. 185)[3]

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pleading because the updated pleading made no substantive changes to PGDx's inequitable conduct counterclaims."))

[2] Additional factual background information regarding the Motions will be addressed in Section III.

[3] In Civil Action No. 17-1623-LPS-CJB, on August 22, 2019, after briefing on the Motion in that case was completed, Plaintiff filed what it titled a "Notice of Subsequent Activity Concerning Guardant's Motion to Dismiss." (Civil Action No. 17-1623-LPS-CJB, D.I. 345) This was a two-page brief in which Plaintiff made additional argument about a subsequent development that had occurred after the close of briefing, which (according to Plaintiff) supported grant of its Motion. (*Id.*) However, Plaintiff did not obtain leave of Court to file this additional brief. And the brief did more than simply provide "citation of subsequent authorities[.]" D. Del. LR 7.1.2(b). Thus, the filing violated D. Del. LR 7.1.2(b), and the Court ORDERS that it be STRICKEN. The Court will not consider its contents, nor the contents of

Although FMI's answering brief is different in form from PGDx's answering brief, the substance of the Defendants' arguments in their respective briefs are largely the same. For this reason, the Court will largely discuss the Motions together below, and it will refer to the "D.I." numbers in Civil Action No. 17-1623-LPS-CJB unless otherwise indicated.

II. STANDARD OF REVIEW

When presented with a Rule 12(b)(6) motion to dismiss for failure to state a claim, a court conducts a two-part analysis. *Fowler v. UPMC Shadyside*, 578 F.3d 203, 210 (3d Cir. 2009). First, the court separates the factual and legal elements of a claim, accepting "all of the complaint's well-pleaded facts as true, but [disregarding] any legal conclusions." *Id.* at 210-11. Second, the court determines "whether the facts alleged in the complaint are sufficient to show that the plaintiff has a 'plausible claim for relief.'" *Id.* at 211 (quoting *Ashcroft v. Iqbal*, 556 U.S. 662, 679 (2009)). "A claim has facial plausibility when the plaintiff pleads factual content that allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Iqbal*, 556 U.S. at 678.

In assessing the plausibility of a claim, the court must "'construe the complaint in the light most favorable to the plaintiff, and determine whether, under any reasonable reading of the complaint, the plaintiff may be entitled to relief.'" *Fowler*, 578 F.3d at 210 (quoting *Phillips v. Cnty. of Allegheny*, 515 F.3d 224, 233 (3d Cir. 2008)). As such, a well-pleaded complaint may not be dismissed simply because "it strikes a savvy judge that actual proof of [the alleged] facts is improbable, and that a recovery is very remote and unlikely." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 556 (2007) (internal quotation marks and citation omitted). Determining whether a

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PGDx's letter filed thereafter (in which, *inter alia*, PGDx objected to Plaintiff's filing). (Civil Action No. 17-1623-LPS-CJB, D.I. 346)

claim is plausible is "'a context-specific task that requires the reviewing court to draw on its judicial experience and common sense.'" *Fowler*, 578 F.3d at 211 (quoting *Iqbal*, 556 U.S. at 679).

III. DISCUSSION

As noted above, Plaintiff's Motions seek dismissal of Defendants' respective counterclaims alleging unenforceability of the '992 patent.[4] Below, the Court will first summarize Defendants' factual allegations relevant to the counterclaims at issue. Thereafter, the Court will assess the parties' arguments regarding the Motions.

A. Relevant Factual Allegations

In its pleadings, Defendants assert that while he was still working at Illumina in 2012, Dr. Eltoukhy obtained information from Illumina documents that reflected all of the elements of the inventive solution touted in the patents-in-suit—i.e., the use of "communication theory" to help reduce or eliminate errors in the process of detecting mutations in cell-free DNA ("cfDNA"). (D.I. 284 at ¶¶ 14-18, 22-26; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶¶ 31-40)[5] Defendants allege that Dr. Eltoukhy shared this information with Guardant co-founder Dr. AmirAli Talasaz, and that the two men thereafter used this information to conceive of the claimed inventions in the patents-in-suit. (D.I. 284 at ¶ 26; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶¶ 31-40)

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[4] Plaintiff does not challenge, at this stage, Defendants' inequitable conduct counterclaims regarding the other three patents-in-suit.

[5] Any citations herein to specific paragraphs in the respective relevant Answers and Counterclaims are to the portions of those pleadings that contain the counterclaims.

From there, Defendants allege that Dr. Eltoukhy and Dr. Talasaz intentionally deceived the United States Patent and Trademark Office ("USPTO"), when they identified Dr. Talasaz as the sole inventor on Guardant's first two provisional patent applications filed in September 2012 (application number 61/696,734, filed on September 4, 2012, and application number 61/704,400, filed on September 21, 2012).[6] (D.I. 284 at ¶ 39; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶¶ 57-58) Defendants assert that the reason why Dr. Eltoukhy and Dr. Talasaz failed to disclose Dr. Eltoukhy's inventorship was that Dr. Eltoukhy was still employed at the time by Illumina; by omitting Dr. Eltoukhy's role, the men allegedly sought to ensure that Guardant (not Illumina) would have full ownership and exclusive rights to the patents-in-suit in the future. (D.I. 284 at ¶ 39; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶ 58) Defendants further allege that Dr. Eltoukhy and Dr. Talasaz went on to make affirmative misrepresentations to the USPTO when they: (1) identified Dr. Talasaz as the sole inventor on documents submitted to the USPTO with the applications that led to the issuance of the '731 patent, the '743 patent and the '822 patent; and (2) thereafter failed to identify Dr. Eltoukhy as an inventor to the USPTO and "suppressed facts and evidence regarding [Dr.] Eltoukhy's inventorship that should have been brought to the USPTO's attention." (D.I. 284 at ¶¶ 41-43; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶¶ 59-61)

Defendants ultimately assert that Dr. Eltoukhy's and Dr. Talasaz's conduct, discussed above, renders unenforceable the claims of the '731 patent, the '743 patent and the '822 patent. (D.I. 284 at ¶¶ 44-49; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶¶ 69-73) And with regard to the '992 patent, which is at issue in these Motions, Defendants allege:

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[6] These applications are listed on the front of the '992 patent and the other three patents-in-suit in the "Related U.S. Application Data" section. (D.I. 280, exs. 1-4)

> Eltoukhy and Talasaz's broad pattern of inequitable conduct was also directly related to the '992 [p]atent, rendering the claims of that patent unenforceable as well. There is a significant relationship between and among the '731, '822, '743 and '992 [p]atents. The '992 [p]atent shares an almost identical specification to the '731, '822 and '743 patents, and relies on the earlier disclosed subject matter for written description support for its claims. By not naming Eltoukhy as an inventor on the '731, '822 and '743 [p]atents, Eltoukhy and Talasaz concealed that Eltoukhy also invented the fundamental ideas underlying the '992 [p]atent.

(D.I. 284 at ¶ 50; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶ 74)

Lastly, Defendants do make somewhat different allegations in their pleadings regarding one issue relevant to the instant Motions: the priority date of the '992 patent. PGDx alleges that all four of the patents-in-suit claim priority to the two September 2012 provisional applications referenced above (the "September 2012 applications" or the "September 2012 provisional patent applications"). (D.I. 284 at ¶ 40) FMI, however, alleges that the '992 patent claims priority to a provisional patent application that Plaintiff filed on March 5, 2014 (application number 61/948,530) (the "March 2014 application" or the "March 2014 provisional patent application").[7] (Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶ 42)[8]

B. Discussion

Defendants' theory as to the unenforceability of the '992 patent is not primarily based on inequitable conduct said to have occurred during the '992 patent's prosecution itself. Instead, it rests on the relationship between the '992 patent and the prosecution of other related patent

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[7] This application is also listed on the front of the '992 patent in the "Related U.S. Application Data" section. (D.I. 280, ex. 4)

[8] As to the other three patents-in-suit, FMI alleges (similar to PGDx) that they claim priority to the September 2012 applications. (Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶ 39)

applications—i.e., on what is known as the doctrine of "infectious unenforceability." (D.I. 284 at ¶¶ 39-40, 50; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶¶ 14-19, 45, 51, 74; D.I. 308) In light of this, before the Court addresses the parties' specific arguments regarding the Motions, it is first worth stepping back to discuss the infectious unenforceability doctrine (and the related law regarding inequitable conduct) more generally.

The law of inequitable conduct finds its origins in the unclean hands doctrine. *See Robocast, Inc. v. Apple Inc.*, 39 F. Supp. 3d 552, 570 (D. Del. 2014) (citing *Consol. Aluminum Corp. v. Foseco Int'l Ltd.*, 910 F. 2d 804, 812 (Fed. Cir. 1990)). The unclean hands doctrine applies where "some unconscionable act of one coming for relief has immediate and necessary relation to the equity that he seeks in respect of the matter in litigation." *Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 245 (1933); *see also Robocast, Inc.*, 39 F. Supp. 3d at 570. The United States Court of Appeals for the Federal Circuit has found that "'inequitable conduct' is no more than the unclean hands doctrine applied to particular conduct before the PTO." *Consol. Aluminum*, 910 F.2d at 812.

Inequitable conduct regarding any single claim in the prosecution of a patent renders the entire patent unenforceable, not just that claim. *Therasense, Inc. v. Becton, Dickinson and Co.*, 649 F.3d 1276, 1288-89 (Fed. Cir. 2011) (en banc). Moreover, the taint of a finding of inequitable conduct can affect not just the improperly-prosecuted patent, but can also "render unenforceable other related patents and applications in the same technology family." *Id.*; *Consol. Aluminum*, 910 F.2d at 808-12. This concept is what courts have referred to as the doctrine of "infectious unenforceability." *See, e.g.*, *Int'l Bus. Machs. Corp. v. Priceline Grp. Inc.*, Civil Action No. 15-137-LPS-CJB, 2017 WL 1349175, at *20 (D. Del. Apr. 10, 2017) (citation omitted)); *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, Civ. No. 08-

309-JJF-LPS, 2009 WL 4928024, at *9 (D. Del. Dec. 18, 2009), *report and recommendation adopted*, 2010 WL 2990039 (D. Del. July 22, 2010); *see also Robocast, Inc.*, 39 F. Supp. 3d at 570 n.10 (noting that while the Federal Circuit has recognized this legal concept, it has not yet "adopted [the] moniker [of 'infectious unenforceability'] as its own")).

Pursuant to this infectious unenforceability doctrine, inequitable conduct associated with one patent may render a related patent unenforceable—so long as the inequitable conduct at issue bears "an immediate and necessary relation" to the enforcement of the related patent. *See, e.g.*, *Consol. Aluminum*, 910 F.2d at 810-11; *Hoffman-La Roche, Inc. v. Promega Corp.*, 319 F. Supp. 2d 1011, 1017 (N.D. Cal. 2004). An "immediate and necessary relation" requires that "the inequitable conduct that occurred earlier in the chain [of issued patents] 'must be related to the targeted claims of the ultimately-issued patent or patents sought to be enforced.'" *eSpeed, Inc. v. Brokertec USA, L.L.C.*, 417 F. Supp. 2d 580, 595 (D. Del. 2006), *aff'd*, 480 F.3d 1129 (Fed. Cir. 2007) (quoting *Semiconductor Energy Lab., Inc. v. Samsung Elecs. Co.*, 24 F. Supp. 2d 537, 543 (E.D. Va. 1998)); *Truth Hardware Corp. v. Ashland Prods., Inc.*, No. Civ.A. 02-1541 GMS, 2003 WL 22005839, at *1 (D. Del. Aug. 19, 2003).

With this legal background now set out, the Court turns to the merits. In that regard, Plaintiff makes three distinct arguments for dismissal. First, Plaintiff notes that as to the '992 patent (unlike with the other three patents-in-suit), Dr. Eltoukhy is actually listed as an inventor on the face of the patent. It therefore argues that there "can [] be no inequitable conduct with respect to the '992 [p]atent based on misnaming of inventors because it is undisputed that the right inventors are named." (D.I. 285 at 3; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 169 at 3) Second, Plaintiff asserts that Defendants' counterclaims must fail because there is not a sufficient relationship "between the alleged inequitable conduct at issue and the *prosecution* of

the ['992 patent]." (D.I. 285 at 4 (certain emphasis omitted, certain emphasis added)); *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 169 at 4) And third, Plaintiff argues that differences between the '992 patent and the other patents-in-suit also preclude a finding of infectious unenforceability here. (D.I. 285 at 4-6; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 169 at 4-6) The Court will address each argument in turn.

1. The Fact that Dr. Eltoukhy is Listed as an Inventor on the '992 Patent Does Not Preclude a Finding that the Patent is Unenforceable.

Plaintiff's first argument—that Defendant's counterclaim fails because Dr. Eltoukhy is listed as an inventor on the '992 patent—is not dispositive. This is because, as noted above, Defendants' theory as to the unenforceability of the '992 patent is not based on inequitable conduct in the '992 patent prosecution itself. Instead, the theory relies on the premise that inequitable conduct with regard to other, previously-filed patent applications is sufficiently related to the enforcement of the '992 patent, such that the '992 patent is also unenforceable.

Furthermore, as PGDx persuasively argues, if Dr. Eltoukhy and Dr. Talasaz *are* guilty of inequitable conduct with regard to the prosecutions of the other patents-in-suit, then the mere act of listing Dr. Eltoukhy as an inventor on the '992 patent would not amount to a sufficient cure for that wrongdoing. (D.I. 308 at 14-15) Merely disclosing, in a subsequent patent application, material that was previously withheld with intent to deceive the USPTO does not "save[] the later issued patent from the consequences of the misconduct." *Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 1571-72 (Fed. Cir. 1983); *see also Truth Hardware Corp.*, 2003 WL 22005839, at *2. Instead, to adequately cure any inequitable conduct that occurred during prosecution, the applicant would have to: (1) expressly advise the PTO of the existence of the misrepresentation; (2) advise the PTO of what the actual facts are and make clear that further examination in light thereof may be required if any PTO action has been based on the

misrepresentation; and (3) establish patentability on the basis of the factually accurate record. *Id.*; *see also Truth Hardware Corp.*, 2003 WL 22005839, at *2; *eSpeed, Inc.*, 417 F. Supp. 2d at 596. Plaintiff makes no assertion that it has met these "curing" requirements. Instead, its argument is that there was no inequitable conduct in the first place—or that even if there was, for other reasons, the doctrine of infectious unenforceability does not apply here as to the '992 patent.

So for these reasons, Plaintiff's first argument for dismissal must fail.

2. Infectious Unenforceability Does Not Require Relation of the Inequitable Conduct to the *Prosecution* of the Challenged Patents.

Plaintiff's next argument for dismissal is that Defendants' counterclaims fail to sufficiently plead infectious unenforceability because that doctrine "requires a relationship between the alleged inequitable conduct and *the prosecution of [the '992 patent]*"; Plaintiff argues that no such relationship exists here. (*See, e.g.*, D.I. 285 at 4 (certain emphasis omitted, certain emphasis added)) In fact, however, the law on infectious unenforceability requires no direct linkage between the inequitable conduct at issue and the prosecution of the patent-in-question. This is clear to the Court for at least three reasons.

First, Plaintiff's position to the contrary is undercut by the Federal Circuit's description of the doctrine of infectious unenforceability. For example, in *Consolidated Aluminum Corp. v. Foseco International Ltd.*, 910 F. 2d 804 (Fed. Cir. 1990), the Federal Circuit stated that to invoke this doctrine, there must be more than "mere relatedness of subject matter" between the patent as to which the patentee committed inequitable conduct and the patent-at-issue. 910 F.2d at 810-11. The *Consolidated Aluminum* Court explained, however, that if there was an "immediate and necessary relation" between the inequitable conduct and the "*equity* [the patentee now] seeks, namely *enforcement* of the [patent(s)-at-issue,]" this would be sufficient to

meet the doctrine's requirements. (*Id.* (internal quotation marks and citation omitted) (emphasis added)); *see also* D.I. 308 at 13; Civil Action No. 17-1616-LPS-CJB, D.I. 179 at 7-8)[9] In light of this, in various Federal Circuit and district court opinions where infectious unenforceability is found to be at play, the courts have made no mention of any direct linkage between (1) the inequitable conduct that occurred during prosecution of the infectious patent and (2) what happened during the *prosecution* of the patent(s)-at-issue. *See, e.g.*, *Agfa Corp. v. Creo Prods. Inc.*, 451 F.3d 1366, 1379 (Fed. Cir. 2006) (finding that inequitable conduct occurring during the prosecution of a parent patent's application infected a later-issued patent, because the later-issued patent was a continuation patent whose subject matter was not sufficiently distinct from that of the parent; in doing so, the Court made no mention of any misconduct occurring during the prosecution of the continuation patent itself); *see also IOENGINE, LLC v. PayPal Holdings,*

[9] In *Consolidated Aluminum*, one of the patents-in-suit (the "'917 patent") was directed to an improved method of filtering molten material. 910 F.2d at 811. The Federal Circuit found that the patent applicant's inequitable conduct in withholding the best mode of a claimed aqueous ceramic slurry during the prosecution of the '917 patent also rendered unenforceable three separate patents-in-suit that covered related subject matter. To that end, the *Consolidated Aluminum* Court concluded that the "inequitable conduct in prosecuting the [infectious '917] patent had 'immediate and necessary relation' . . . to the equity [plaintiff] [sought], namely enforcement of the [three other, related patents-in-suit]." *Id.* at 810-11. This was so because the patentee's concealment of the best mode (the "CS1-B slurry") during prosecution of the infectious patent allowed the patent applicant to present the CS1-B slurry as part of the invention disclosure in the specification of one of the three later-issued patents (the "'081 patent"). *Id.* at 811. And because, *inter alia*, the other two patents' applications were continuations-in-part of the '081 patent application and both included reference to the CS1-B slurry in their claims, they too were rendered unenforceable due to the inequitable conduct occurring regarding the '917 patent. *Id.* at 812. In these ways, the *Consolidated Aluminum* Court found that the patent owner's inequitable conduct in concealing the CS1-B slurry from the '917 patent "permeated the prosecution of the other patents-in-suit [rendering] them unenforceable." *Id.*

Inc., Civil Action No. 18-452-WCB, 2019 WL 2121395, at *4-5 (D. Del. May 15, 2019) (Bryson, J., sitting by designation); *Truth Hardware Corp.*, 2003 WL 22005839, at *2.[10]

Second, requiring an "immediate and necessary relation" between the inequitable conduct at issue and the prosecution of the allegedly infected patent(s)-in-suit (as opposed to the "enforcement" of such patents more generally) would seem to render the doctrine of infectious unenforceability superfluous. As Defendants argue, "requiring a finding that withheld information from an earlier application be 'material to the *prosecution* of the child application' would 'eviscerate the infectious unenforceability doctrine' in that it would be 'no different than traditional inequitable conduct pleading.'" (D.I. 308 at 13 (emphasis in original) (quoting *Eon Corp. IP Holdings, LLC v. T-Mobile USA, Inc.*, CASE NO. 6:10-CV-379-LED-JDL, 2011 WL 13134896, at *7 (E.D. Tex. Dec. 13, 2011), *report and recommendation adopted*, 2012 WL 12893881 (E.D. Tex. Jan. 18, 2012)); *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 179 at 12-13)

Third, the single Federal Circuit case that Plaintiff relies on in support of its argument here—*Pharmacia Corp. v. Par Pharmaceutical, Inc.*, 417 F.3d 1369 (Fed. Cir. 2005)—is inapposite. (D.I. 285 at 4-5) In *Pharmacia*, the Federal Circuit made clear that the defendant had "*not* asserted on appeal" the type of infectious unenforceability claim that Defendants are now pressing here: "that the [allegedly-infected] patent is unenforceable under a general unclean hands theory; i.e., that a broad pattern of inequitable conduct transfers inequitable conduct from

[10] Defendants also argue that even if a relationship with the prosecution of the allegedly-infected patent is required, they have made such a showing here. (D.I. 308 at 13-14; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 179 at 3-4, 11 n.9) Because the Court finds that no such showing is required in order to invoke the infectious unenforceability doctrine, it need not address Defendants' arguments in this regard.

one patent to another." 417 F.3d at 1374 (emphasis added) (citing *Consol. Aluminum*, 910 F.2d at 812). Instead, the defendant in *Pharmacia* was making a very different argument, asserting that: (1) because the patentee had filed terminal disclaimers on the applications of two patents-at-issue, these disclaimers "b[ound the] two related patents together"; and thus (2) inequitable conduct occurring during the prosecution of the allegedly-infectious patent (the "'368 patent")—but *after the issuance* of the allegedly-infected patent (the "'504 patent")—nevertheless had "automatically infect[ed]" the *earlier-issued* '504 patent. *Id.* at 1374-75.

The *Pharmacia* Court ultimately concluded (affirming a district court's decision issued after a bench trial) that this type of "reverse infectious inequitable conduct" allegation, (Civil Action No. 17-1616-LPS-CJB, D.I. 179 at 8), could not serve to render the '504 patent unenforceable. 417 F.3d at 1374-75. In articulating the basis for its decision, the Federal Circuit stated in part that "[b]ecause the record shows no inequitable conduct during *prosecution of the* [earlier-issued, challenged] '504 patent itself, the district court did not abuse its direction in finding [that] patent to be valid and enforceable." *Id.* at 1375 (emphasis added). Plaintiff relies on this statement here, suggesting that it means that for infectious enforceability to apply, there must be inequitable conduct shown to relate to the "prosecution of the" '922 patent. But that is a misreading of *Pharmacia*, as the next sentence of that opinion states "[i]n fact, the '504 patent had already issued before the inequitable conduct occurred." *Id.* When read in context, it is clear that the *Pharmacia* Court's decision (and the language it used, set out above) was meant to refer to the unique circumstances before it—i.e., to convey that since there had been no inequitable conduct during the prosecution of the '504 patent, *and because the '504 patent had already issued*, then one could not utilize later-occurring inequitable conduct to render that patent retroactively unenforceable. In contrast, here the inequitable conduct argument at issue is

a very different one—involving allegations that inequitable conduct occurred *during the prosecution of earlier-prosecuted patent applications*, which thus infects the patentee's ability to enforce a *later-issued* patent. For this reason, Plaintiff's citation to *Pharmacia* is not helpful to it here.

For all of these reasons, the Court rejects Plaintiff's second argument for dismissal.

3. The Relationship Between the Inequitable Conduct Occurring as to the '731, '743 and '822 Patents and the Enforcement of the '992 Patent Indicates that the Motions Should be Denied.

Lastly, Plaintiff asserts that the doctrine of infectious unenforceability is inapplicable here because there are too many differences between the inequitable conduct said to have occurred with regard to the '731, '743 and '822 patents on the one hand, and the enforcement of the '992 patent on the other hand.

The Court disagrees. Instead, it concludes that Defendants have pleaded sufficient facts to demonstrate the required "immediate and necessary relation" between the inequitable conduct at issue and the targeted claims of the '992 patent, in light of: (1) the close relationship between the content of the respective patents and the inequitable conduct allegations at issue; and (2) what is plausibly alleged regarding the family history and the priority relationship of the respective patents. Below, the Court discusses each of these two bases in turn.

a. The Close Relationship Between the Content of the Respective Patents and the Inequitable Conduct Allegations at Issue

Defendants persuasively allege that the patents-in-suit are closely related in substance, which ultimately helps their argument against dismissal.

For example, Defendants allege that there are great similarities between the *specifications* of the four patents, in that they are "almost identical[.]" (D.I. 284 at ¶ 50; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶ 45) This is essentially the case, as the only apparent

substantive difference between the specifications appears to be the addition of some material to the '992 patent disclosure that was not included in the disclosures for the other three patents. That material relates to non-unique identifiers and how, in some embodiments, ligation conditions can be utilized that can result in certain thresholds of ligation efficiency; it is set out in two columns of the 60+ column '992 patent disclosure. (*See* '992 patent, cols. 41:24-43:12) Accordingly, the abstracts of the patents-in-suit are word-for-word identical, and each of the patents contains the exact same figures. (D.I. 280, exs. 1-4); *see also Cognex Corp. v. VCode Holdings, Inc.*, Civ. No. 06-1040 (JNE/JJG), 2008 WL 2113661, at *27 (D. Minn. May 19, 2008) (noting that the claims of the patent-at-issue had an immediate and necessary relation to the inequitable conduct that had occurred in the prosecution of an earlier related patent application, where the patents' disclosures were "essentially identical" and the patents shared "almost identical written descriptions with identical diagrams"); *eSpeed, Inc.*, 417 F. Supp. 2d at 595 (noting the "strikingly similar" natures of the disclosures of the two patents-at-issue, in concluding that the doctrine of infectious unenforceability was applicable). It is also significant that the title of each patent is the same: "SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION." (D.I. 280, exs. 1-4)

Additionally, Defendants allege that the *claims* of the patents-in-suit are intimately related. In particular, Defendants pleaded that the claims of the patents-in-suit all relate to a "communication theory[,]" which allows for reduced errors in the amplification and sequencing of cfDNA when conducting a "liquid biopsy." (D.I. 284 at ¶¶ 14-18; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶¶ 14-19 (referring to the allegedly-"innovative method" as "Digital Sequencing"), 31-33, 45, 51, 74) They also allege that the claims of all four patents—including at least independent claim 1 of the '992 patent—implement this "communication

theory" solution by invoking particular steps (including the tagging of sequence reads, the grouping of sequence reads with the same tags into families and the collapsing the sequence reads to create "consensus sequences"). (D.I. 284 at ¶ 18 (citing claims in each of the four patents-in-suit, including claim 1(b)-(f) of the '992 patent); *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶ 33 (noting the same three steps and asserting that they "closely resemble the elements of Guardant's patented method"); *id.* at ¶¶ 45, 51 (similarly describing the "inventions claimed in each of the asserted patents" and noting that the inventions are captured in, *inter alia*, claim 1 of the '992 patent)); *see also eSpeed, Inc.*, 417 F. Supp. 2d at 596 (noting the "close relation" of the asserted claims of the two patents-at-issue). In light of this, if Defendants' assertion is that the patentee committed inequitable conduct by failing to disclose Dr. Eltoukhy's inventorship role with regard to certain aspects of the "communication theory" solution—and if those same purportedly inventive aspects make up a key part of the claims of the '992 patent—then this appears to persuasively demonstrate a close relationship between the inequitable conduct at issue and "the targeted claims of the ultimately-issued patent or patents sought to be enforced." *eSpeed, Inc.*, 417 F. Supp. 2d at 595 (internal quotation marks and citation omitted); *see also* (Civil Action No. 17-1616-LPS-CJB, D.I. 179 at 12-13 n.10).

Lastly, the prosecution history of the '992 patent shows that its claims are directed to very similar subject matter to that covered by at least one of the other three patents-in-suit. (D.I. 308 at 6, 9) During the prosecution of the '992 patent, the Examiner issued a double-patenting rejection of the '992 patent over the '731 patent. (D.I. 308, ex. 1 at 5-6, 12-14) To overcome this rejection, Plaintiff filed a terminal disclaimer. (*Id.*, ex. 2 at 1-2) Thus, the Examiner believed that the claims of the '992 patent were not "patentably distinct" from the claims of the '731 patent, *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985), and the applicant chose not to then-

challenge the Examiner's view. *See Cognex Corp.*, 2008 WL 2113661, at *27 (D. Minn. May 19, 2008) (finding that the claims of the purportedly infectious patent and the claims of the later-issued patent were "sufficiently related" for purposes of infectious unenforceability, in part because the patentees filed a terminal disclaimer as to the later-issued patent, avoiding the rejection of that patent's claims over the infectious patent's claims).[11] This is another indicator that the alleged inequitable conduct, which is said to have directly related to Guardant's ability to capture the inventions set out in the '731 patent, bears and immediate and necessary relation to the content of the claims of the '992 patent.

For all of these reasons, the significant overlap in the content of the respective patents (and, relatedly, the relationship between the inequitable conduct allegations at issue and the enforcement of the '992 patent), supports Defendants' position here.

b. The Allegations Regarding the Family History and Priority Relationship of the Respective Patents

[11] Plaintiff argues that the terminal disclaimer "means nothing in this context," citing *Pharmacia* in support. (D.I. 315 at 7) However *Pharmacia* does not stand for the broad proposition that terminal disclaimers are never relevant to an assertion of infectious unenforceability. As was noted above, the *Pharmacia* Court made clear that the defendant in that case (unlike here) had not asserted that the challenged patent was "unenforceable under a general unclean hands theory[.]" 417 F.3d at 1374. Instead, there the defendant was attempting to use the terminal disclaimer to argue that inequitable conduct in procuring a *later-prosecuted* patent automatically infected an *earlier-issued* patent. The *Pharmacia* Court rejected this proposition, finding that in those circumstances, "something more than a naked terminal disclaimer is required." *Id.* Here, in contrast, Defendants are asserting that inequitable conduct as to *earlier-issued* patents infects a *later-issued* patent, as the '992 patent issued on February 27, 2018, after the other three patents-in-suit issued. (D.I. 280, exs. 1-4) And, of course, as cited above, Defendants rely on much more to make this case than the "naked" fact of the terminal disclaimer described above.

The Court next assesses the facts of record regarding the family history and priority relationship between the '992 patent and the other three patents. Before doing so, it is useful to assess how the law treats such information in assessing infectious unenforceability claims.

Our Court, relying on prior Federal Circuit precedent, has noted that if a patentee commits inequitable conduct during prosecution of one patent, then a later continuation patent will almost surely be found to bear an "immediate and necessary relation" to the patent obtained by way of the inequitable conduct. *Robocast, Inc.*, 39 F. Supp. 3d at 571; *see also IOENGINE, LLC*, 2019 WL 2121395, at *4-5. This is in significant part because continuation applications are understood to "relate to the same invention." *Robocast, Inc.*, 39 F. Supp. 3d at 571 (noting that "[i]f the same patentee split the claims into two applications, why should the result be any different?" and that "[t]o hold otherwise would fly in the face of the rule that inequitable conduct renders all claims unenforceable, 'not just the particular claims to which the inequitable conduct is directly connected.'") (quoting *J.P. Stevens & Co., Inc. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1561 (Fed. Cir. 1984)).[12] And more generally, with regard to the invocation of the infectious unenforceability doctrine, courts have found that if the patent-at-issue is linked to an infectious patent (or application) through a common claim of priority, this fact also helps to establish the requisite "immediate and necessary relation." *See Eon Corp.*, 2011 WL 13134896, at *7 (denying a motion to dismiss an inequitable conduct counterclaim based on the doctrine of infectious unenforceability, in part because the allegations were that plaintiff claimed priority for

[12] On the other hand, our Court has noted that a divisional application may be "drawn to a different invention, and different inventions do not share an 'immediate and necessary' relation to each other." *Robocast, Inc.*, 39 F. Supp. 3d at 571 (citing *Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1332 (Fed. Cir. 1998)); *see also IOENGINE, LLC*, 2019 WL 2121395, at *4 (citing *Baxter Int'l, Inc.*, 149 F.3d at 1332).

the patent-at-issue based on the infectious patent); *eSpeed, Inc.*, 417 F. Supp. 2d at 596 (finding, after a bench trial, that the patent-at-issue was unenforceable because, *inter alia*, it "claim[ed] priority from the [infectious] application").

The Court now turns to the record here on this topic. It is a bit of a mess.

On the one hand, in its counterclaims, PGDx alleges that all four patents-in-suit, including the '992 patent, claim priority to the two Guardant September 2012 provisional patent applications. (D.I. 284 at ¶¶ 39-40) These two provisional applications are listed on the front page of the '992 patent as "Related U.S. Application Data" (just as they are so listed on the front page of the other three patents-in-suit). (D.I. 280, exs. 1-4) And at various points in the prosecution history of the '992 patent (including as recently as via a June 2019 filing in an *inter partes* review proceeding regarding that patent—a filing made just days before the instant Motions were filed), *Guardant* affirmatively represented to the USPTO that the '992 patent in fact claims priority to the September 2012 provisional applications. (Civil Action No. 17-1616-LPS-CJB, D.I. 179, exs. 1-2)[13] In light of this, PGDx argues in its briefing that the "'992 [p]atent [] arises from a continuation-in-part application that claims priority to many of the same earlier applications as the other three patents-in-suit." (D.I. 308 at 9)

FMI, however, appeared to take a different tack in its counterclaims. There, it alleged that '992 patent claims priority to Guardant's *March 2014 provisional patent application* and did not mention the September 2012 applications in its discussion of the '992 patent's priority date.

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[13] These cited exhibits were attached to Defendants' respective answering briefs. (D.I. 308, exs. 3-4; Civil Action No. 17-1616-LPS-CJB, D.I. 179, exs. 1-2) The Court can consider such exhibits (and others referenced herein that are part of the patents-in-suit's prosecution history), as a patent's prosecution history is a public record that may be taken into account in resolving a motion to dismiss. *See Int'l Bus. Machs. Corp.*, 2016 WL 626495, at *20 n.18 (citing cases).

(Civil Action No. 17-1616-LPS-CJB, D.I. 168 at ¶ 42) Yet in its briefing, FMI seemed to now align itself with PGDx's position that: (1) the '992 patent claims priority to the September 2012 provisional patent applications; and (2) the '992 patent is a continuation-in-part of an application that led to the grant of the other three patents-in-suit. (Civil Action No. 17-1616-LPS-CJB, D.I. 179 at 10 (FMI arguing that "Guardant's '992 patent resulted from continuations and continuations-in-part of the original applications which were the subject of the inequitable conduct alleged by FMI in this litigation."))

As for Plaintiff, in its briefing, it now takes the position that "the '992 Patent derives priority from [the March 2014 provisional application] as opposed to the other three asserted patents which derive priority from [the Guardant provisional application] filed a year and a half earlier on September 4, 2012." (D.I. 285 at 4; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 169 at 4) Plaintiff argues that it has made this same contention in responding to certain interrogatories during the instant litigations. (D.I. 285 at 4 & ex. 2; Civil Action No. 17-1616-LPS-CJB, D.I. 169 at 4 & ex. 1) And although it acknowledges that this contention is directly contradictory to the priority-date-related statements it made to the USPTO in the past, Plaintiff asserts that as of July 2019, it has sought to correct those statements (which it now calls "inadvertent error") with the USPTO. (D.I. 315 at 7 & ex. 1; Civil Action No. 17-1616-LPS-CJB, D.I. 185 at 8 & ex. 2)[14]

[14] It its reply briefs, Plaintiff for the first time explains *why* it is that it believes the '992 patent "can only derive support from the later 2014 Application." (D.I. 315 at 5; *see also* Civil Action No. 17-1616-LPS-CJB, D.I. 185 at 6) There, it asserts that this is because: (1) each of the claims of the '992 patent require ligation "compris[ing] using more than 10x molar excess of the adaptors as compared to the cfDNA molecules, thereby generating tagged parent polynucleotides"; (2) this concept was invented by Dr. Stephanie Mortimer, a listed inventor on the '992 patent (who is not listed as an inventor on the other three patents-in-suit) and thus is referenced only in the '992 patent specification; and (3) since this limitation "was only disclosed

Taking the entirety of this (confused) record into account, the Court concludes that it is at least plausible that the '992 patent shares a September 2012 priority date with the other three patents. This is because the record demonstrates that: (1) the relevant September 2012 provisional applications are listed on the front of the '992 patent; (2) the '992 patent shares deep similarities with the other three patents-in-suit that claim priority to this same 2012 date; and (3) as late as days prior to the filing of the Motions, even Plaintiff was asserting (in another forum) that the four patents all share that same priority date. Of course, it may well be that this is not the case, and that the '992 patent is entitled only to a March 2014 priority date instead. But the correct priority date for a patent is an issue that may turn on the resolution of disputed facts. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-07 (Fed. Cir. 2008); *Johns Hopkins Univ. v. 454 Life Scis. Corp.*, 183 F. Supp. 3d 563, 574-78 (D. Del. May 2, 2016); *SimpleAir, Inc. v. AWS Convergence Techs., Inc.*, Case No. 2:09-cv-289, 2012 WL 12978274, at *2 (E.D. Tex. Apr. 3, 2012).[15]

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and described in the 2014 Application, it would not have been possible for Guardant to file a patent application on this subject matter prior to 2014." (*Id.*)

The substance of this more detailed argument should have been included in Plaintiff's opening briefs, but was not. Thus, in their answering briefs, Defendants did not address this argument. As a result, the Court will not consider the details of this argument in resolving the instant Motions. D. Del. LR 7.1.3(c)(2) ("The party filing the opening brief shall not reserve material for the reply brief which should have been included in a full and fair opening brief."); *see also Lab. Skin Care, Inc. v. Ltd. Brands, Inc.*, 757 F. Supp. 2d 431, 439 (D. Del. 2010); *Rockwell Techs., LLC. v. Spectra-Physics Lasers, Inc.*, No. CIV.A.00-589 GMS, 2002 WL 531555, at *3 (D. Del. Mar. 26, 2002).

[15] Even if the '992 patent, in fact, is not entitled to the same priority date as the other three patents-in-suit, precedent does not appear to strictly require identity of priority for infectious unenforceability to apply. Instead, priority claims linking the infectious/infected patents appear to be merely a factor for courts to consider in this analysis.

Moreover, it is at least clear from the "Related U.S. Application Data" listed on the front page of each of the patents that they are all part of the same genealogical chain. (D.I. 280, exs. 1-4) That familial relationship is also evidence of the close relationship of the subject matter of the '992 patent and that of the other three patents-in-suit.

4. Conclusion

Defendants have pleaded facts demonstrating an extremely close connection between the content of the '992 patent and the other patents-in-suit (and, relatedly, between the nature of the inequitable conduct allegations and the content of the '992 patent's claims). Additionally, there are at least sufficient facts pleaded to plausibly allege that the four patents are part of the same family and that they all share the same priority date. Taking all of this together, Defendants have sufficiently alleged that the '992 patent is unenforceable pursuant to the doctrine of infectious unenforceability.

IV. CONCLUSION

For the foregoing reasons, the Court recommends that Plaintiff's Motion be DENIED.

This Report and Recommendation is filed pursuant to 28 U.S.C. § 636(b)(1)(B), Fed. R. Civ. P. 72(b)(1), and D. Del. LR 72.1. The parties may serve and file specific written objections within fourteen (14) days after being served with a copy of this Report and Recommendation. Fed. R. Civ. P. 72(b)(2). The failure of a party to object to legal conclusions may result in the loss of the right to de novo review in the district court. *See Henderson v. Carlson*, 812 F.2d 874, 878-79 (3d Cir. 1987); *Sincavage v. Barnhart*, 171 F. App'x 924, 925 n.1 (3d Cir. 2006).

The parties are directed to the Court's Standing Order for Objections Filed Under Fed. R. Civ. P. 72, dated October 9, 2013, a copy of which is available on the District Court's website, located at http://www.ded.uscourts.gov.

Because this Report and Recommendation may contain confidential information, it has been released under seal, pending review by the parties to allow them to submit a single, jointly proposed, redacted version (if necessary) of the Report and Recommendation. Any such redacted version shall be submitted no later than **January 10, 2020**, for review by the Court, along with a motion for redaction that includes a clear, factually detailed explanation as to why disclosure of any proposed redacted material would "work a clearly defined and serious injury to the party seeking closure." *Pansy v. Borough of Stroudsburg*, 23 F.3d 772, 786 (3d Cir. 1994) (internal quotation marks and citation omitted). The Court will subsequently issue a publicly-available version of its Report and Recommendation.

Dated: January 7, 2020

Christopher J. Burke
UNITED STATES MAGISTRATE JUDGE

EX1002.526

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GUARDANT HEALTH, INC. Plaintiff, v. FOUNDATION MEDICINE, INC. Defendant.	)	C.A. No. 17-1616-LPS-CJB
GUARDANT HEALTH, INC. Plaintiff, v. PERSONAL GENOME DIAGNOSTICS, INC. Defendant.	)	C.A. No. 17-1623-LPS-CJB

MEMORANDUM ORDER

WHEREAS, on September 11, 2019, Magistrate Judge Burke issued a Report and Recommendation (C.A. No. 17-1616 ("1616") D.I. 212; C.A. No. 17-1623 ("1623") D.I. 359) ("September Report") recommending that the Court adopt certain claim constructions for two disputed terms in United States Patent Nos. 9,598,731 (the "'731 patent"), 9,834,822 (the "'822 patent"), 9,840,743 (the "'743 patent") and 9,902,992 (the "'992 patent" and collectively with the other patents, "the asserted patents");

WHEREAS, on September 25, 2019, Defendants Foundation Medicine, Inc. ("FMI")

and Personal Genome Diagnostics, Inc. ("PGDx") (collectively, "Defendants") filed objections to the September Report (1616 D.I. 228; 1623 D.I. 378) ("Defs. Sept. Obj."), specifically objecting that (1) Judge Burke erred in not construing the terms "consensus sequence"[1] and "collapsing sequence reads in each family"[2] and (2) PDGx's proposed constructions of these terms should be adopted;

WHEREAS, on October 9, 2019, Plaintiff Guardant Health, Inc. ("Guardant" or "Plaintiff") filed a response to Defendants' Objections (1616 D.I. 237; 1623 D.I. 387) ("Pl. Sept. Resp.");

WHEREAS, on October 11, 2019, Judge Burke issued a Report and Recommendation (1616 D.I. 239; 1623 D.I. 389) ("October Report") recommending that the Court adopt certain claim constructions for two disputed term sets in the asserted patents;

WHEREAS, on October 25, 2019, Defendants filed objections to the October Report (1616 D.I. 251; 1623 D.I. 397) ("Defs. Oct. Obj."), specifically objecting that (1) the claim terms "detecting, at one or more loci, at least one single nucleotide variant, at least one gene fusion and at least one copy number variant"[3] and "detecting, at one or more genetic loci, a plurality of genetic aberrations, wherein the plurality of genetic aberrations comprises two or more different members selected from the group of members consisting of a single base substitution, a copy number variation (CNV), and insertion or deletion (indel), and a gene fusion"[4] (the "Detecting Terms") are indefinite; (2) Judge Burke failed to address

[1] This term appears in claim 1 of the '731 patent.

[2] This term appears in claim 1 of the '822 patent and claim 1 of the '992 patent.

[3] This term appears in claim 2 of the '822 patent.

[4] This term appears in claim 1 of the '992 patent.

Defendants' arguments about the scope of the Detecting Terms; and (3) the claim constructions proposed by Guardant and adopted by Judge Burke are indefinite;

WHEREAS, on November 8, 2019, Guardant filed a response to Defendants' Objections (1616 D.I. 264; 1623 D.I. 405) ("Pl. Oct. Resp.");

WHEREAS, on October 25, 2019, Guardant also filed objections to the October Report (1616 D.I. 255; 1623 D.I. 399), specifically objecting that Judge Burke erred in concluding that the claim terms "beginning" and "end" (the "Sequencing Terms")[5] are indefinite ("Pl. Oct. Obj.");

WHEREAS, on November 8, 2019, Defendants filed a response to Guardant's Objections (1616 D.I. 265; 1623 D.I. 406) ("Defs. Oct. Resp.");

WHEREAS, on November 1, 2019, Judge Burke issued a Report and Recommendation (1616 D.I. 260; 1623 D.I. 402) ("November Report"), recommending that the Court adopt certain claim constructions for four disputed terms in the asserted patents;

WHEREAS, on November 15, 2019, Defendants filed objections to the November Report (1616 D.I. 269; 1623 D.I. 411) ("Defs. Nov. Obj."), specifically objecting that the claim term "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject"[6] should not encompass the sequencing of amplicons of extracellular polynucleotides;

WHEREAS, on December 2, 2019, Guardant filed a response to Defendants' Objections (1616 D.I. 283; 1623 D.I. 424) ("Pl. Nov. Resp.");

WHEREAS, on November 15, 2019, Guardant also filed objections to the November

[5] These terms appear in claim 1 of the '731 patent and claims 19-20 of the '992 patent.

[6] This term appears in claims 1 and 10 of the '743 patent.

Report (1616 D.I. 270; 1623 D.I. 412) ("Pl. Nov. Obj."), specifically objecting that (1) Judge Burke's construction of the claim term "each parent polynucleotide"[7] contradicted the intrinsic record and (2) Judge Burke's construction of the claim terms "grouping the plurality of sequence reads produced from each non-uniquely tagged parent polynucleotide into families," "grouping the sequence reads into families," and "grouping the sequence reads mapped in e) into families" (the "Grouping Terms")[8] improperly required that every generated sequence read into families;

WHEREAS, on December 2, 2019, Defendants filed a response to Guardant's Objections (1616 D.I. 282; 1623 D.I. 423);

WHEREAS, the Court has considered the parties' claim construction disputes addressed by the September Report, October Report, and November Report *de novo*, *see St. Clair Intellectual Prop. Consultants, Inc. v. Matsushita Elec. Indus. Co., Ltd.*, 691 F. Supp. 2d 538, 541-42 (D. Del. 2010); 28 U.S.C. § 636(b)(1); Fed. R. Civ. P. 72(b)(3);

WHEREAS, on January 7, 2020, Judge Burke issued a Report and Recommendation (1616 D.I. 343; 1623 D.I. 470) ("January Report") recommending that the Court deny Guardant's motions to dismiss (1616 D.I. 169; 1623 D.I. 285) the inequitable conduct counterclaims filed by FMI and PGDx;

WHEREAS, on January 21, 2020, Guardant filed Objections to the January Report (1616 D.I. 373; 1623 D.I. 505) ("Pl. Jan. Obj."), specifically objecting that the parties' summary judgment briefing mooted the January Report and that the evidence did not support Defendants' counterclaims;

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[7] This term appears in claim 1 of the '731 patent.

[8] These terms appear in claim 1 of the '731 patent, claim 1 of the '822 patent, and claim 1 of the '992 patent, respectively.

WHEREAS, on February 4, 2020, Defendants filed a response to Guardant's Objections (1616 D.I. 385; 1623 D.I. 525) ("Def. Jan. Resp.");

WHEREAS, the Court has reviewed *de novo* the portions of the January Report relating to the dispositive issues of dismissal and adequacy of the pleadings, *see Brown v. Astrue*, 649 F.3d 193, 195 (3d Cir. 2011); 28 U.S.C. § 636(b)(1); Fed. R. Civ. P. 72(b)(3);

NOW THEREFORE, IT IS HEREBY ORDERED that:

A. the September Report is ADOPTED in full and Defendants' Objection to it is OVERRULED;

B. the October Report is ADOPTED in all respects EXCEPT with respect to the recommendation that the Sequencing Terms be found indefinite, Defendants' Objection to it is OVERRULED, and Plaintiff's Objection to it is SUSTAINED;

C. the November Report is ADOPTED in full and Defendants' and Plaintiff's Objections to it are OVERRULED; and

D. the January Report is ADOPTED in full, Plaintiff's Objection to it is OVERRULED, and Plaintiff's motions to dismiss (1616 D.I. 169; 1623 D.I. 285) are DENIED.

1. With respect to the September Report, Defendants argue that the Court should construe claim terms to which Judge Burke accorded "plain and ordinary" meaning because the parties' purported disputes over these terms are "now ripe." (1616 D.I. 228 at 6; 1623 D.I. 378 at 6) At least in the context of the instant case, this is not a meritorious basis to object to the September Report. The Report persuasively explains why, based on the arguments made to Judge Burke and the evidence before him, the claim terms "consensus sequence" and "collapsing sequence reads in each family" should be given their plain and ordinary meaning to a person having ordinary skill in the art ("POSA"). For example, the

claims themselves explain that "consensus sequences" are determined by "comparing the sequence reads grouped within each family to each other" and that each one "corresponds to a unique polynucleotide," '731 patent at 62:37-42, and the process of "collapsing sequence reads in each family" will "yield a base call for each family at the genetic locus," '822 patent at 62:43-46. It appears that the parties' dispute as to whether a single base may be a "consensus sequence" (*compare, e.g.*, Defs. Sept. Obj. at 5 *with* Pl. Sept. Resp. at 9) is a fact question for the jury (i.e., a question of infringement and/or invalidity). However, if it ultimately appears to the Court that this is properly understood as a dispute of claim scope, the Court will undertake additional claim construction at some later date. *See generally Stryker Corp. v. Zimmer, Inc.*, 837 F.3d 1268, 1276 (Fed. Cir. 2016) (contemplating "rolling claim construction, in which the court revisits and alters its interpretation of the claim terms as its understanding of the technology evolves"); *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1360 (Fed. Cir. 2008) ("When the parties raise an actual dispute regarding the proper scope of these claims, the court, not the jury, must resolve that dispute.").

2. With respect to the October Report, Defendants argue that the Detecting Terms are indefinite because "the specification and the claims are at odds with one another, and thus a person of ordinary skill in the art would have found that the inventions set forth [in these claims] are not what the inventors regarded as their invention." (Defs. Oct. Obj. at 4) (internal quotation marks omitted) The Court, like Judge Burke, disagrees. The claim describes an invention that can "detect[], at one . . . genetic loci, a plurality of generic aberrations" while the specification, not inconsistently, provides that the invention can, at a single locus, identify and track individual molecules that exhibit multiple mutations. (*See,*

e.g., Pl. Oct. Resp. at 4-5) Defendants' expert acknowledged that a person of ordinary skill in the art could use the invention to detect several mutations at one locus. (*Id.* at 5) Further, in connection with their invalidity challenges, Defendants have been able to identify the "literal meaning" of the claim terms – that the invention "cover[s] the unexpected scenario of detecting multiple mutation types at a single locus," undermining the contention that a POSA would fail to have reasonable certainty as to claim scope. (Pl. Oct. Resp. at 5) (citing Defendants' expert stating POSA could use claimed invention to detect multiple mutations at one locus) Defendants have not shown by clear and convincing evidence that the Detecting Terms (nor the recommended constructions of them) are indefinite.

3. Guardant objects to the October Report's recommendation that the Sequencing Terms are indefinite, insisting that Defendants "did not show by clear and convincing evidence that these plain and ordinary words could not be understood by the skilled artisan with reasonable certainty." (Pl. Oct. Obj. at 1) The Court's *de novo* review leads it to conclude this is a fact dispute, not amenable here to resolution at the claim construction stage. The Court does not believe that, at the claim construction stage, Defendants produced evidence that would necessarily persuade all reasonable factfinders that a POSA would be unable to determine, with reasonable certainty, the scope of the disputed claims. For instance, Defendants' expert, Dr. Stacey Gabriel, provided testimony that could reasonably be interpreted as supporting a finding that the Sequencing Terms are ***not*** indefinite. (*See, e.g.*, Pls. Oct. Obj. at 6-8) (citing evidence) This portion of the October Report is NOT ADOPTED.[9]

[9] The Court is troubled that Plaintiff failed to provide the required certification that its objections do not raise new legal or factual arguments, or alternatively identifying the new arguments and showing good cause for failing to raise them with the Magistrate Judge. (*See* Standing Order (Oct. 9, 2013) ¶ 5; *see also* Defs. Oct. Resp. at 1-3) In the context of the instant

4. With respect to the November Report, Defendants argue that term "sequencing extracellular polynucleotides from a bodily sample from [a/the] subject" does not encompass amplicons because amplicons are created outside the body. However, the specification repeatedly suggests that the claimed invention can involve the sequencing of amplicons. *See, e.g.,* '743 patent at 33:39-40 ("Typically, polynucleotides in a tagged library are amplified and the resulting amplified molecules are sequenced."); *id.* at 33:65-66 (noting that "certain embodiments . . . provide[] sequence-tagged nucleotides, that [are] amplified and sequenced"). Excluding amplicons from the construction is improper also because dependent claims 3 and 12 of the '743 patent encompass the sequencing of amplicons. *See* '743 patent at 63:1-3, 64:3-5; *see also Trustees of Columbia Univ. in City of N.Y. v. Symantec Corp.*, 811 F.3d 1359, 1370 (Fed. Cir. 2016) ("[W]here dependent claims have no meaningful difference other than an added limitation . . . construing the independent claim to exclude material covered by the dependent claim would be inconsistent."); *see also* Pl. Nov. Resp. at 5-7 (citing testimony of Defendants' non-infringement experts). Additionally, FMI argued in an IPR petition that this term was anticipated by prior art that discloses the sequencing of amplicons, further supporting the conclusion that this claim term does encompass amplicons. *See generally Research Frontiers, Inc. v. E Ink Corp.*, 2016 WL 1169580, at *3 n.4 (D. Del. Mar. 24, 2016), *report and recommendation adopted in* 2016 WL 7217217 (D. Del. Dec. 13, 2016).

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case, however, the Court is not persuaded that the proper consequence of Plaintiff's procedural failing is the invalidation of a patent that this Court, on *de novo* review, believes could well be found to be not indefinite. The Court's conclusion in this regard is informed by the facts that (i) Plaintiff's "heav[y] reli[ance] on new portions of the specification that it has never previously cited," as Defendants attack Plaintiff for doing (Defs. Oct. Resp. at 3; *see also id.* at 6) is not the kind of abusive practice the Standing Order is principally directed to; and (ii) the Court would reach the same conclusion it has here even if it did not consider any of Plaintiff's new evidence or argument.

5. Turning to Plaintiff's objections to the November Report, the Court agrees with Judge Burke that the term "each parent polynucleotide" should be construed as "every one of the parent nucleotides from step (c)." The claim language itself, "each parent polynucleotide" plainly means "every one of the parent polynucleotides," an understanding the specification repeatedly confirms. *See, e.g.,* '731 patent at 5:36-41; *id.* at 42:32-36. While Guardant points to specification embodiments that may be outside of the claim as so construed, "the claims of the patent need not encompass all disclosed embodiments." *TIP Sys., LLC v. Phillips & Brooks/Gladwin, Inc.*, 529 F.3d 1364, 1373 (Fed. Cir. 2008).[10] Guardant's emphasis on the claim term "comprising" does not alter the Court's conclusion, as "comprising" "permit[s] additional elements not required by a claim," but it "does not remove the limitations that are present." *Power Mosfet Techs., L.L.C. v. Siemens AG*, 378 F.3d 1396, 1409 (Fed. Cir. 2004). Even assuming (but not deciding) Guardant could show good cause for its reliance on expert depositions and reports it did not put before Judge Burke, the Court is not persuaded that any of this new material conflicts with the recommended construction. The Court also disagrees with Guardant's contention that Judge Burke construed the Grouping Terms "too narrowly." (Pl. Nov. Obj. at 7) Because definite articles such as "the" can be "anaphoric phrases, referring to the initial antecedent phrase," the Court (like Judge Burke) reads the claim terms "grouping the plurality of sequence reads" and "grouping the sequence reads" as referring to the set of sequence reads discussed in the prior step. *See Baldwin Graphic Sys., Inc. v.*

[10] In general, the Court agrees with Guardant that "[a] construction that renders infringement impossible using the very devices disclosed in the specification for use with the invention cannot be right." (Pl. Nov. Obj. at 1) However, here, Plaintiff has not persuaded the Court that this general principle provides a meritorious basis to reject the recommended construction, given the particular claim language being construed and Defendants' seeming agreement that "the Illumina system [disclosed in the specification] ***could*** carry out the claimed invention." (Defs. Nov. Resp. at 8 n.4)

Siebert, Inc., 512 F.3d 1338, 1342-43 (Fed. Cir. 2008). The Court is also not persuaded by Guardant's argument that dependent claim 5 of the '731 patent, which provides for "filtering out sequence reads," shows that "certain sequence reads will not be analyzed and not placed into groups." (Pl. Nov. Obj. at 8) The independent claims at issue here – none of which includes a filtering step – all require grouping every sequence described in the prior steps, and any additional step cannot eliminate this express limitation. *See Power Mosfet,* 378 F.3d at 1409. The deposition testimony cited by Guardant relates only to prior art and claim 5 of the '731 patent as well as claim 10 of the '822 patent; it does not address the independent claims at issue here nor undermine the express meaning of the claim limitations.

6. Finally, turning to the January Report, the Court disagrees with Guardant that the parties' summary judgment briefing necessarily renders that Report moot. The parties have a ripe dispute as to whether Defendants' counterclaims adequately allege inequitable conduct, and now also have a dispute as to whether Defendants can survive Guardant's summary judgment motion. Guardant fails in its objections to articulate how Judge Burke's recommendation that Defendants adequately state a plausible claim for inequitable conduct is wrong. (*See* Pl. Jan. Obj. at 1) (asserting, in conclusory manner, "[t]he facts pleaded by Defendants are not sufficient to show a plausible claim for relief") The Court has reviewed Judge Burke's thorough January Report *de novo* and agrees that Defendants have stated a plausible claim.

March 23, 2020
Wilmington, Delaware

HONORABLE LEONARD P. STARK
UNITED STATES DISTRICT JUDGE

Paper No. ___
Filed: December 4, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FOUNDATION MEDICINE, INC.,
Petitioner,

v.

GUARDANT HEALTH, INC.,
Patent Owner.

Case IPR2019-00634
Patent No. 9,840,743

PATENT OWNER RESPONSE
PURSUANT TO 37 C.F.R. § 42.120

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IX.APPENDIX 54

I. INTRODUCTION

It is now clear that genomes are not the stable places they were once thought. Genome-wide studies over the last decade have revealed the phenomenon of copy number variations—an unexpectedly frequent, dynamic and complex form of genetic diversity. Copy number variants are structurally variant sub-chromosomal regions in which copy number differences have been observed between two or more individuals or in one individual over time.

The involved U.S. Patent No. 9,840,743 ("the '743 patent")(EX1001) provides methods for detecting these copy number variation mutations.

The Board instituted *inter partes* review (paper 10) of claims 1-26 of the '743 patent based on Grounds 1 and 2 in a petition filed by Foundation Medicine, Inc. ("Petitioner"). The Board also instituted with respect to Grounds 3 and 4 of the petition based on *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359-60 (2018) and corresponding USPTO Guidance (April 26, 2018), even though the Board concluded that Petitioner had not demonstrated a reasonable likelihood of success with respect to Grounds 3 and 4. Paper 10, 31-33.

Many of the arguments in Grounds 1 and 2 are staked to a flawed narrative that copy number variation and chromosomal aneuploidy refer to the same genetic aberration. The '743 patent is directed to detecting the former. "Copy number variation" is the term recited in claim 1, the only independent claim in Grounds 1

and 2. The '743 specification describes copy number variation and aneuploidy as different genetic aberrations. Indeed, aneuploidy is not recited in any of the claims.

The claim construction portion of the Institution Decision adopted an argument embedded in the petition materials that copy number variation includes aneuploidy. Paper 10, 9-11. This construction was incorrect because it deviates from the intrinsic record of the '743 patent. It is well settled that claims themselves provide substantial guidance as to the meaning of particular claim terms. The claims, of course, must be read in view of the specification, and the '743 specification describes copy number variation and aneuploidy as distinct genetic aberrations. Petitioner's expert testified on cross-examination that she did not even review the specification of the '743 patent for its definition of copy number variation, nor had she been asked to conduct such a review. *E.g.* EX2022, 72:12-73:7.

Extrinsic evidence is viewed by the courts as "less significant than the intrinsic record in determining the legally operative meaning of claim language." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)). Yet that is precisely what Petitioner's expert relied on in reaching her opinion and then relied upon in the Decision. EX1002, ¶27 (citing EX1026); Paper 10, 9-10 (citing EX1002, ¶27 and exhibits therein).

The construction adopted in the Decision is also incorrect because it renders the claims nonsensical. As explained by Patent Owner's expert, Dr. Carlos Bustamante, if copy number variation is interpreted so broadly as to include aneuploidy, the recited method is not capable of detecting aneuploidy. As Dr. Bustamante discusses in more detail in his declaration (EX2023, ¶¶43, 59, 61), for example, the claim 1, step "e)i)", of "normalizing a number of reads in the plurality of predefined regions to each other" would yield no information about aneuploidy. The Federal Circuit has rejected claim construction that is inconsistent with the specification and that would result in illogical or nonsensical methods or subject matter. *E.g. Ring Plus, Inc. v. Cingular Wireless Corp.*, 614 F.3d 1354, 1364 (Fed. Cir. 2010).

The issues noted above with respect to copy number variation also apply to the construction of the claim term "predefined region." This term was interpreted inconsistent with the intrinsic evidence, i.e., its usage in the claims and the specification of the '743 patent. Dr. Gabriel testified on cross-examination that she did not review the '743 patent with a view toward interpreting the construction of "predefined region." EX2022, 72:12-24. The petition materials interpreted the term as encompassing an entire chromosome without conducting any analysis. The usage in the claims is clear, however, that it could not encompass an entire chromosome, and as Dr. Bustamante explains in his testimony, as with copy

number variation, such an interpretation would render the claims illogical. EX2023, ¶¶43, 59, 61.

Regardless of the claim construction issues, to anticipate a claim under §102 a reference must still contain all the elements of a claim, arranged in the manner of the claim. As Dr. Bustamante explains in his testimony, the reference relied upon in Ground 1, Chiu et al. ("Chiu," EX1033), is clearly missing at least one element of claim 1, step "e)i)", "normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other." In view of context of the entirety of claim 1, step e) is about determining the copy number variation in one or more of the plurality of predefined regions. Even if it was assumed that the predefined region is a chromosome (though it would render the claim illogical), step e)i) alone cannot be used to determine the aneuploidy based on Chiu's method. The section of Chiu related to step e)i) that the Petitioner highlights determines the percentage of total reads in a maternal plasma sample that can be attributed to a particular chromosome. Based on Petitioner's assumption that a predefined region is a whole chromosome, this step alone is not sufficient to determine aneuploidy. Ground 1 falls far short of the requisite showing for §102 anticipation.

Ground 2 of the petition is missing the same element in its analysis. Even though a combination of references are asserted under 35 U.S.C. §103 (Kinde 2012

and Kinde 2011), the references are required to teach at least in combination each and every element of the claims. A missing claim limitation defeats an assertion of unpatentability. As with Chiu, Kinde 2012 and Kinde 2011 even when combined are missing the elements of step "e)i)," "normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other." This omission makes it impossible to complete an obviousness analysis.

The challenges of the petition fail to rise to a *prima facie* case of unpatentability. Accordingly, as discussed in greater detail below and the accompanying evidence, the petition's unpatentability assertions against the claims of the '743 patent should be denied.

As part of the evidence submitted in support of this Patent Owner Response are declarations by Dr. Carlos Bustamante (EX2023) and Dr. John Quackenbush (EX2026). Dr. Bustamante is presently a professor of Biomedical Data Science, Genetics, and Biology at Stanford University. He also served as the Inaugural Chair of the Department of Biomedical Data Sciences from 2015-2019. He joined Stanford University in 2010, where his research has focused on clinical and medical genomics on a global scale. EX2023, ¶4. Prior to Stanford, he was a full tenured professor at Cornell University, having joined Cornell in 2002, where he was also Associate Director of the Cornell Center for Comparative and Population

Genomics. His work primarily focused on population genetics and agricultural genomics. *Id.*, ¶3. He earned his B.A., M.S. and Ph.D. from Harvard University, and served as a post-doctoral fellow at the University of Oxford. *Id.*, ¶2.

Dr. Bustamante has authored or co-authored numerous articles and publications and is a named inventor on several patents, shown in his curriculum vitae. EX2023, ¶¶8-9; EX2025. He has served on the boards or advisory boards of various corporations, non-profit entities, and government organizations, as well as numerous editorial boards in the field. EX2023, ¶¶5-7. For his work in the field, Dr. Bustamante has received several honors and fellowships, including the MacArthur "Genius" Award (2010), a Marshall-Sherfield Scholarship to Oxford (2001-2), and the Stanford Prize in Population Genetics and Society (2016). Dr. Bustamante is well qualified as an expert, possessing the necessary scientific, technical, educational and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing the expertise necessary to determine and explain the level of ordinary skill in the art as of September 4, 2012.

Dr. Quackenbush is the Henry Pickering Walcott Professor of Computational Biology and Bioinformatics and Chair of the Department of Biostatistics at the Harvard T.H. Chan School of Public Health. EX2026, ¶2. He is also Director of the MS Program in Computational Biology and Quantitative

Genetics and Director of the Big Data to Knowledge Training Program, and holds appointments as Professor of Biostatistics and Computational Biology at the Dana-Farber Cancer Institute and at the Channing Division of Network Medicine of Brigham and Women's Hospital. *Id.*

Prior to joining the faculty at Dana-Farber and Harvard in 2005, Dr. Quackenbush was a Professor of Chemical Engineering at the University of Maryland from 2003-2005; an Investigator with The Institute for Genomic Research from 2002-2006; a Professor in the Department of Biochemistry at The George Washington University from 2000-2005; a Lecturer in The Department of Biostatistics at The Johns Hopkins University from 1998-2005; an Associate Investigator at The Institute for Genomic Research from 1997-2001; and an Assistant Investigator at The Institute for Genomic Research in 1997. EX2026, ¶6. He obtained his Ph.D. in Theoretical Particle Physics at the University of California, Los Angeles in 1990, and holds a Master of Science in Physics from University of California, Los Angeles and a Bachelor of Science in Physics from the California Institute of Technology. *Id.*, ¶7.

Dr. Quackenbush has published more than 290 peer reviewed scientific papers that have been cited more than 71,000 times. EX2026, ¶10. He has served on the boards or advisory boards of various corporations, non-profit entities, and government organizations. *Id.*, ¶¶3-4. Dr. Quackenbush is well-qualified as an

expert, possessing the necessary scientific, technical, educational and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing the expertise necessary to determine and explain the level of ordinary skill in the art as of September 4, 2012. Dr. Quackenbush's *curriculum vitae* is provided as EX2027.

II. THE CHALLENGED CLAIMS

Claim 1 is representative of the challenged claims, and is directed to methods for detecting copy number variation in extracellular polynucleotides obtained from a subject, and is reproduced below.

> 1. A method for detecting copy number variation, comprising:
>
> a) sequencing extracellular polynucleotides from a bodily sample from a subject, wherein each of the extracellular polynucleotides generates a plurality of sequence reads;
>
> b) filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold;
>
> c) mapping the plurality of sequence reads to a reference sequence;
>
> d) quantifying mapped reads or unique sequence reads in a plurality of predefined regions of the reference sequence; and
>
> e) determining copy number variation in one or more of the plurality of predefined regions by:
>
> i) normalizing a number of reads in the plurality of predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other; and/or

ii) processing a number of reads in the plurality of predefined regions or a number of unique sequence reads in the plurality of predefined regions with numbers obtained from a control sample.

III. CLAIM CONSTRUCTION

The claim terms should be given their ordinary and customary meaning, consistent with the specification, as a person of ordinary skill in the art ("POSA") understood them. 37 C.F.R. § 42.100(b); *Phillips*, 415 F.3d at 1313; *see also* Consolidated Trial Practice Guide (November 2019) at 45-46 (noting that the claim construction standard now used at the PTAB is the same as that as used by Article III Federal Courts, which follow *Phillips*).

Claim construction begins with the claim language itself. *Vitronics Corp. v. Conceptronic*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("First, we look to the words of the claims themselves"). Next, the specification should be reviewed to assess "whether the inventor has used any terms in a manner inconsistent with their ordinary meaning." *Id.* "Usually, [the specification] is dispositive" as "it is the single best guide to the meaning of a disputed term." *Id.*; *see also Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1360 (Fed. Cir. 2004) ("In most cases, the best source for discerning the proper context of claim terms is the patent specification wherein the patent applicant describes the invention.").

Petitioner did not identify any specific constructions for any claim terms in the section of the petition titled "claim construction." Pet. 16-17. The arguments in the grounds of challenge, however, embedded interpretations of various claim terms in its analysis of the grounds such that the cited prior art was said to fall within the scope of the challenged claims. This much is acknowledged in the petition and the arguments are a claim construction even though not specifically identified as such by the petition. Pet. 16. Specifically, the petition materials were based on an unreasonably broad and unfounded interpretation of "predefined regions" as encompassing entire chromosomes, and of "copy number variation" encompassing chromosomal aneuploidy. *E.g.* Pet. 24 and 34.

In the Preliminary Response, Patent Owner pointed out how those implicit constructions offered by Petitioner were inconsistent with the specification of the '743 patent. The Board, however, adopted Petitioner's constructions for the purposes of Institution. But as Dr. Bustamante testifies, when considered in view of the intrinsic evidence of the '743 patent claims and specification, both the Board's and Petitioner's constructions are unreasonably broad. *See also* EX2023, ¶¶30-47.

These claim terms and how they would be construed by the ordinary artisan in view of the language of the claims themselves, as well as the specification, are discussed below. Notwithstanding these constructions, however, evidence is

presented here demonstrating that the challenged claims of the '743 patent are not unpatentable in view of the applied art.

A. Predefined region

Each ground of challenge is based on an unstated assumption that the claim term "predefined region" encompasses an entire chromosome. *E.g.*, Pet. 26 (noting that Chiu discloses that "[t]he number of sequence reads originating from any particular chromosome was then counted and tabulated for each human chromosome."). The petition materials provide no citation to the '743 patent and no explanation for why a POSA would understand "predefined region" to encompass an entire chromosome. Notably, Dr. Gabriel confirmed on cross-examination that she did not take the specification of the '743 patent into account, and that she had not been asked to do so. *E.g.* EX2022, 72:12-24.

As discussed, claim construction begins with the language of the claims themselves. Construing "predefined region" as encompassing an entire chromosome leads to a nonsensical result for the claimed method. That is, this method does not make sense at the chromosomal level. *E.g.*, EX2023, ¶¶43, 59, 61.

Specifically, claim 1, step e)1) requires "normalizing a number of reads in the plurality predefined regions to each other, or a number of unique sequence reads in the plurality of predefined regions to each other." Petitioner would like to ignore the language "in the plurality predefined regions to each other, or a number

of unique sequence reads in the plurality of predefined regions," and specifically, the requirement that the reads in the plurality of defined regions are normalized to each other. *E.g.* Pet. 22 (characterizing the claim language as "normalizing a number of reads … to each other"). However, it is axiomatic that every word in the claim must be given meaning. *See Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006) (explaining that claim language "should not [be] treated as meaningless."); *Unique Concepts, Inc. v. Brown,* 939 F.2d 1558, 1562 (Fed. Cir. 1991) ("All the limitations of a claim must be considered meaningful.")

The ordinary artisan would understand that if the predefined regions encompass an entire chromosome, one would not be determining copy number variation in the chromosome itself. EX2023, ¶42. In the case of aneuploidy, the ordinary artisan would understand that one is trying to determine the entire prefined region, that is, the entire chromosome. *Id.* Thus, the express use of the language of the claim itself in step e)i) of normalizing the number of reads "in the predefined regions" excludes a construction in which "predefined region" is read as encompassing a chromosome. The same analysis applies to step e)ii) of claim 1, as it also recites the language "a number of reads in the plurality of predefined regions."

Even if the word "in" in the claim is not given its appropriate weight and meaning, comparing the sequence reads of one chromosome (i.e., one of a plurality

of predefined regions) to the sequence reads in a second chromosome would fail to yield information about the aneuploidy of either chromosome. That is, as the ordinary artisan would understand, the number of sequence reads for any particular chromosome is dependent on the size of the chromosome. The larger the chromosome, the higher the number of sequence reads. Thus, "normalizing the number of reads in the plurality of predefined regions to each other" may provide information about the relative sizes of the chromosomes, but would not provide any information as to the number of copies of each chromosome in the sample. EX2023, ¶43.

Moreover, the intrinsic record, that is, the claims and specification of the '743 patent, is consistent with the above analysis and does not support Petitioner's overly broad interpretation of "predefined region." The '743 patent specification explains that the claimed "predefined regions" are "at least about 10 kb, 20 kb, 30 kb 40 10 kb, 50 kb, 60 kb, 70 kb, 80 kb, 90 kb, or 100 kb in size." *Id.*, 16:7-12. The specification explains further that "[i]n some embodiments, prededefined regions are uniform or substantially uniform in size, about 10 kb, 20 kb, 30 kb[,] 40 kb, 50 kb, 60 kb, 70 kb, 80 kb, 90 kb, or 100 kb in size. In some embodiments, at least 50, 100, 200, 500, 1000, 2000, 5000, 10,000, 20,000, or 50,000 regions are analyzed." *Id.* 3:61-65. Those sizes of "predefined regions" are inconsistent with that of an entire chromosome. EX2023, ¶45. For example, human chromosome 21,

which is the subject chromosome of references Chiu and Kinde 2012, is over 46 million base pairs. EX2023, ¶45. In addition, the added requirement that the predefined regions are uniform or substantially uniform in size is not consistent with the predefined region encompassing chromosomes, as not all chromosomes are uniform or substantially uniform in size. EX2023, ¶46. The number of predefined regions analyzed, that is, from 50 to 50,000 regions, is are also inconsistent with a construction of "predefined region" as encompassing a chromosome.

Patent Owner recognizes that the above excerpts are drawn to certain embodiments. However, when read in the collective, they clearly reflect an understanding that a "predefined region" does not include a chromosome. Moreover, neither Petitioner nor Dr. Gabriel point to any disclosure in the '734 specification to support the assertion that "predefined regions" includes entire chromosomes.

For the purposes of its Institution Decision, the Board construed predefined region to be "not limited to any specific number of base pairs, but may encompass any predefined region of a genome, including an entire chromosome." Paper 10, 8. Even though the Board noted that, "while the Specification teaches an embodiment where the predefined regions are limited to a specific range of kilobases," it stated that "the Specification also uses the term to encompass larger regions that can

include chromosomes in a genome." *Id.* The Board took out of context language in the '743 specification regarding a step of "selecting predefined regions in a genome," and concluded that a chromosome is part of a genome. *Id.* Patent Owner agrees that a "predefined region" is found in a genome, but this does not mean that it encompasses the genome, or a whole chromosome. Neither petition nor the Board point to anything in the '743 specification that Patentee, or a POSA reading the specification of the '743 patent, would have intended a predefined region to encompass anything as large as an entire chromosome.

The Institution Decision also relied upon the disclosure of the specification that the predefined region may be larger than the disclosed exemplary sizes, and thus may include a chromosome, comparing the disclosure at column 16, lines 9-10 of the patent (reproduced above) and that at column 5, line 22. The specification at column 5 is setting forth a computer readable medium for performing a method that includes a step of "selecting predefined regions in a genome." *Id.*, 5:20-22. This passage is in no way defining what is meant by a "predefined region," whereas the disclosures of the specification discussed above are clearly providing guidance as to the size and the number of predefined regions. Thus, the Board's reliance on *Johnson Worldwide Assoc. Inc., v. Zebco Corp.*, 175 F.3d 985 (Fed. Cir. 1999) is inapposite, as the specification does not use the term in varied ways,

as the smaller sizes specified by the specification are not at odds with the fact that those regions are also part of the genome.

Accordingly, the construction of "predefined region" as it would be understood by the ordinary artisan in view of the specification is that it does not encompass an entire chromosome. EX2023, ¶44.

B. Copy number variation

Claim 1 of the '743 patent is directed to "a method for detecting copy number variation." EX1001, Claim 1, preamble, step e).

The petition materials urge that "aneuploidy is a type of copy number variation that refers to the presence of an abnormal number of chromosomes." Pet. 5 (citing EX1002, ¶27; EX1026, 1048; EX1028, 444; EX1029, 189-91). But Petitioner provides no explanation for why a POSA would consider the term "copy number variation" to encompass aneuploidy in the context of the '743 patent specification.

For the purposes of its Institution Decision, the Board agreed with Petitioner and construed "copy number variation" to include aneuploidy. Paper 10, 10. The Board (Paper 10, 10) cited a paper by Sehnert (EX1026) for its disclosure of a method "capable of detecting any aneuploidy or other copy number variation." That disclosure, however, is more consistent with usage in the '743 patent that aneuploidy and copy number variation are distinct entities.

The Board relied also on the declaration testimony of Dr. Gabriel to the effect that "the ordinary meaning of the term 'copy number variation' would embrace aneuploidy." *Id.* Surprisingly, however, Dr. Gabriel did not cite to anything in the '743 patent specification to support her opinion. EX1002, ¶27. In fact, she subsequently testified at deposition that she did not consider usage of "copy number variation" in the context of the '743 patent specification in forming her opinion, nor had she been asked to when she was preparing her declaration:

Q. Yes. Let's look at Paragraph 27.
In Paragraph 27 you state that
"aneuploidy is the type of copy number
variation that refers to the presence of an
abnormal of chromosomes."
A. (Nodding.) Yes.
Q. Do you say anything in the intrinsic
record to support that understanding that
aneuploidy is a type of copy number
variation?
MS. SCHONEWALD: Objection.
A. I don't think I felt it was necessary
to cite anything. I think it's just an
understanding of one of skill in the art.
Q. Did you look at the intrinsic record
in the '743 patent to find out if it makes
a distinction between aneuploidy and copy
number variation?
MS. SCHONEWALD: Objection.

A. I wasn't asked to do that specifically, so I did not do that.

EX2022, 68:10-69:6 (emphasis supplied).

"Copy number variation" and "aneuploidy" are discussed in the '743 patent specification as distinct genetic aberrations. *E.g.*, EX1001, 52:15-20 ("These system and methods may be used to detect any number of genetic aberrations that may cause or result from cancers. These may include but are not limited to …, ***copy number variations***, transversions, translocations, inversion, deletions, ***aneuploidy***, …") (emphasis added). *See also* EX2023, ¶31. The '743 patent further describes copy number variations as sub-chromosomal aberrations. *Id.*, 7:40-42 ("[T]he genetic variation is copy number/heterozygosity variation and detecting is performed with sub-chromosomal resolution."). Such description is consistent with methods that detect "copy number variations" in "predefined regions" that are much smaller than the size of a single chromosome. Aneuploidies, in contrast, are genetic aberrations in the number of chromosomes. EX2023, ¶31.

The Board, in its Institution Decision, determined that the above passages do not suggest that the identified categories are mutually exclusive. Paper 10, 10. Although the recitation of mutations and rare mutations may include the other listed variations, the Board does not explain why the specification would list both copy number variations and aneuploidy separately if they were not considered to

be different conditions by the inventors. *E.g.* EX1001, 2:53-64. In fact, in discussing looking at possible abnormal conditions that may be present in a fetus, the specification again lists copy number variations and aneuploidy separately, again suggesting that the inventors did not consider copy number variations to be inclusive of aneuploidy. EX1001, 2:65-3:3; EX2023, ¶31. Further, when discussing copy number variations, the specification states:

> In some embodiments, a genetic variant, rare mutation or copy number variation occurs in a region of the genome selected from the group consisting of gene fusions, gene duplications, gene deletions, gene translocations, microsatellite regions, gene fragments or combination thereof. In other embodiments a genetic variant, rare mutation, or copy number variation occurs in a region of genome selected from the group consisting of genes, oncogenes, tumor suppressor genes, promotors, regulatory sequence elements, or combinations thereof. In some embodiments the variant is a nucleotide variant, single base substitution, or small indel, transversion, translocation, inversion, deletion, truncation, or gene truncation about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 nucleotides in length.

EX1001, 3:66-4:12.

As can be seen from the above excerpt, the specification is referring to copy number variation at the gene level, and not the chromosomal level. Notably, in its more specific discussion of copy number variation here, the specification does not mention aneuploidy. And Dr. Bustamante agrees that both the Board's and

Petitioner's constructions of copy number variation are unreasonably broad. EX2023, ¶¶31-40.

Further confirming that copy number variation and aneuploidy are distinct genetic aberrations is the treatment of these terms by relevant public databases—on which the '743 patent expressly relies. For example, the '743 patent is directed to identifying "genetic aberrations that may cause or result from cancers." *E.g.*, EX1001, 52:15-20. The '743 patent identifies COSMIC as a public database that contains sequence information for cancer-specific genetic aberrations including "actionable cancer-related genes." EX1001, 61:16-25; *see also id.*, 60:46- 61:25 (Example 7), 61:1-3 (describing example 7 as capable of detecting CNVs); EX2023, ¶36.

Consistent with the '743 patent, COSMIC describes copy number variations as sub-chromosomal genetic alterations. EX2035. For example, the curators at COSMIC indicate that copy number variations are found **on** chromosomes. EX2035, 1 ("where all the CNVs on this chromosome can be viewed for the sample"). Further, copy number variations are referred to as "alleles." *Id.* A POSA would have understood the term "allele" to refer to a form of a gene. That is, COSMIC identifies copy number variations as sub-chromosomal alterations in the copy number of genes. EX2023, ¶37.

The curators at COSMIC also indicate that copy number variations are annotated in the database using an algorithm known as "ASCAT 2.4" and that this algorithm is described by Loo, et al. EX2035, 1 (citing EX2036). As with COSMIC, Loo describes copy number variations as sub-chromosomal alterations in the copy number of genes. *E.g.*, EX2036, 16914 (Figure 5, showing distribution of copy number variants on chromosomes); *see also* EX2023, ¶38.

Moreover, Loo distinguishes ploidy (i.e., the number of chromosomes) and copy number variation in much the same way as the '743 patent. *E.g.*, EX2036, 16912 ("We define here a copy number-neutral event as an allelic bias for an SNP heterozygous in the germline such that the total copy number does not differ from the tumor ploidy."), 16912-13 ("However, more than a decade later, it remains difficult to determine accurate genome-wide copy number profiles of tumors from these high-throughput arrays. Complicating factors are that tumor cells are often aneuploid (9, 10) …"). EX2023, ¶39.

Accordingly, a POSA would understand that, in view of the specification, the claim term "copy number variant" different from, as not encompassing aneuploidy.

IV. RESPONSE TO GROUND 1

A. Chiu Omits Critical Elements of Claim 1

The Chiu reference is directed to detecting aneuploidy. *E.g.* EX2023, ¶¶48-53. Claim 1 is directed to a method for detecting copy number variation. As discussed above, there is no reasonable claim construction that puts claim 1 in the realm of aneuploidy detection. It should come as no surprise then, regardless of the claim construction issue, that claim 1 contains limitations missing from Chiu. Because an allegedly anticipating reference must contain all limitations found in a claim, under any construction the Chiu reference still fails to anticipate claim 1 and dependent claims 2, 3, and 22-26. *E.g. Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, 296 F.3d 1106, 113 (Fed. Cir. 2002) (It is "improper to broaden the scope of the claimed function by ignoring clear limitations in the claim language."); *Maxwell v. J. Baker, Inc.*, 86 F.3d 1098, 1105 (Fed. Cir. 1996) (rejecting a claim interpretation that ignores explicit limitations in the claim).

The petition charts its theory of how Chiu meets the limitations in claim 1 in a Table set forth on page 22 of the petition, reproduced below:

Limitation of Claim 1 (EX1001)	Depicted in Figure 1 of Chiu (EX1022)
"a) sequencing extracellular polynucleotides from a bodily sample from a subject . . .":	Sequencing cell free DNA fragments from maternal plasma.
"b) filtering out reads that fail to meet a set accuracy, quality score, or mapping score threshold:"	Limiting analysis to "unique sequences." This constitutes filtering out sequence reads that do not map to a unique position, i.e., that do not meet a mapping score threshold. *See infra* VIII.1.B.
"c) mapping the plurality of sequence reads to a reference sequence;"	"Bioinformatics alignment." The legend for Figure 1 also explains: "The chromosomal origin of each [sequence read] was identified through mapping to the human reference genome."
"d) quantifying mapped reads . . . in a plurality of predefined regions of the reference sequence";	"Sequence counting" (counting mapped reads for each predefined region, i.e., each chromosome).
"e) determining copy number variation . . . by:	"Disease status determination."
i) "normalizing a number of reads . . . to each other" ; and	Calculating the % chrN value based on the unique reads for each chromosome and the total unique reads. This is a normalizing calculation. *See infra* VIII.1.F.
ii) "processing a number of reads . . . numbers obtained from a control sample"	Z-score analysis. The legend for Figure 1 explains that "[t]he z-score of a potentially aneuploidy chromosome is expected to be higher for pregnancies with an aneuploidy fetus than for those with a euploid fetus" (the control sample).

In the analysis of step "d)" in the above chart, the petition equates an entire chromosome to a "predefined region" as used in claim 1 ("counting mapped reads for each predefined region, i.e., each chromosome."). This is consistent with usage elsewhere in Ground 1 (*e.g.*, p. 26, "in 'a plurality of predefined regions in the reference sequence' (i.e., chromosomes)"; p. 27, "in a plurality of predefined regions [i.e., chromosomes] to each other," p. 29, "the predefined regions (i.e., chromosomes)."). *See e.g.* EX2023, ¶56. As discussed, there is no reasonable claim

construction under *Phillips* that would allow the "predetermined region" required by claim 1 to read on a chromosome. Petitioner thus fails to demonstrate that Chiu teaches that required element of claim 1, and Petitioner's anticipation analysis fails on that basis alone. EX2023, ¶¶48-67.

In addition, the analysis of step "e)" in the chart omits reference to "one or more of the predefined regions." EX2023, ¶57. This omission highlights a significant difference between what Chiu is doing and the method of claim 1. The claim recites "determining copy number variation in one or more of the plurality of predefined regions." Because Chiu's "predefined region" is an entire whole chromosome (according to the petition), it is not possible to determine copy number variation **in a** predefined region, that is the chromosome; rather, Chiu would be determining copy number **of a** predefined region. Importantly, other than pointing to the normalization of Chiu, the petition fails to explain how that normalization step meets the claim limitation of "normalizing a number of reads in the plurality of predefined regions to each other," or "normalizing … a number of unique sequence reads in the plurality of predefined regions to each other," and thus fails to meet its burden of demonstrating how Chiu anticipated the challenged claim.

This difference becomes even more clear in the discussion of step "e)i)," when the chart again omits the claim language "in the plurality of predefined

regions" and replaces it with "…". EX2023, ¶58. As explained in the chart, Chiu is performing a normalization calculation based on reads "for each chromosome and the total unique reads." The claim states that normalization is occurring, however, among "a number of reads ***in*** the plurality of predefined regions ***to*** each other." The difference is that if chromosomes are the predefined regions, normalizing to other chromosomes would provide no information as to aneuploidy status, defeating the entire purpose of Chiu's teachings. EX2023, ¶59.

At the conclusion of step "e)i)", the analysis in the chart omits the "or" from "and/or," making the processing step "e)ii)" mandatory as applied to Chiu, which is also consistent with the analysis of Chiu in the challenge. The chart again omits reference to "in the plurality of predefined regions" in its two occurrences in step "e)ii)." The chart then finds the processing step of claim 1 to be allegedly met by a Z-score analysis in the legend to Chiu Fig. 1. EX2023, ¶60. When the normalization step is performed with reads "in the plurality of predefined regions to each other," however, followed by Z-score processing as taught by Chiu, meaningful information about aneuploidy is not obtainable. This is because reads in the plurality of predefined regions must be normalized "to each other" as recited in step "e)i)". When different chromosomes are normalized to each other (each being a "predefined region" according to the petition), even with Z-score processing, information relates to the population of chromosomes in general, and

not to any one specific chromosome. Thus, meaningful information regarding aneuploidy would not be obtained. EX2023, ¶61. Petitioner has not demonstrated otherwise.

Obviously intending to morph Chiu into an anticipatory reference by omitting critical claim limitations from its analysis, the petition defeats Chiu's entire purpose of detecting aneuploidy, defeating the anticipation argument as well. Chiu fails to disclose at least step "e)i)" of claim 1, and thus cannot anticipate claim 1 or any of the challenged dependent claims. *In re Royka*, 490 F.2d 981, 984 (CCPA 1974) ("It is elementary that to support an anticipation rejection, all elements of the claim must be found in the reference.").

B. Chiu discloses a method for detecting aneuploidy —not copy number variations

The petition materials state that "Chiu discloses a method for diagnosing a fetal aneuploidy known as Trisomy 21 ('T21')" and that "T21 is a copy number variation." Pet. 20 (citing EX1002, ¶77). Even if true, these assertions are insufficient to establish that Chiu discloses methods "for detecting copy number variation." EX2023, ¶62.

As explained above, the '743 patent specification describes aneuploidy and copy number variations as distinct genetic aberrations. *E.g.*, EX1001, 52:15-20 ("These system and methods may be used to detect any number of genetic aberrations that may cause or result from cancers. These may include but are not

limited to …, ***copy number variations***, transversions, translocations, inversion, deletions, ***aneuploidy***, …") (emphasis added); *see also* Section IV.B. The '743 patent further describes copy number variations as sub-chromosomal aberrations. *Id.*, 7:40-42 ("[T]he genetic variation is copy number/heterozygosity variation and detecting is performed with sub-chromosomal resolution."). Aneuploidies, in contrast, are genetic aberrations in the number of chromosomes. *E.g.*, EX1041, 1 ("The most common aneuploidy is trisomy 21…"); EX2023, ¶63.

Chiu also acknowledges a distinction between aneuploidy and copy number variation and specifically describes a method for detection of aneuploidy. EX1022, 20459 ("We previously proposed that the recently available massively parallel genomic sequencing (MPGS) platforms might be adaptable as an approach to quantify DNA sequences for the noninvasive prenatal diagnosis of fetal chromosomal ***aneuploidy***.") (internal citation omitted). Chiu concedes that, while aneuploidy is detected with its methods, detecting aberrations involving regions less than a whole chromosome would require further modifications and improvements to its methods. *Id.*, 20462 ("[T]he precision and accuracy of MPGS for determining the genomic representation of maternal plasma DNA could be further improved by a number of post-sequencing analysis strategies. For example, sequences occurring in regions of known ***copy number variations*** (25) could be adjusted…"). EX2023, ¶64.

Chiu does not disclose detecting sub-chromosomal aberrations, nor is it sufficiently precise to do so. *See* EX2017, 16 (Chiu has "a description on detection of 'aneuploidy', but no description related to the detection of 'copy number variation'."). EX2023, ¶¶65-66.

That Chiu could possibly detect copy number variants, if substantially modified, is not a sufficient showing for anticipation. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) ("[D]ifferences between the prior art reference and a claimed invention, however slight, invoke the question of obviousness, not anticipation."). Accordingly, for this reason and others, Chiu fails to anticipate claim 1 and its dependent claims 2, 3, and 22-26.

V. RESPONSE TO GROUND 2

Ground 2 combines the references of Kinde 2012 and Kinde 2011, but even as combined, the combination fails to teach all of the limitations of claim 1. *E.g.* EX2023, ¶¶49-52, 68. All other claims at issue in this Ground 2, i.e., claim 2-9, 20, and 22-26, depend directly or indirectly from claim 1. The combined references must teach each element of the claim before even a prima facie case of obviousness arises. *CFMT, Inc. v. YieldUp Int'l Corp.,* 349 F.3d 1333, 1342 (Fed. Cir. 2003)("obviousness requires a suggestion of all limitations in a claim") (citing *Royka,* 490 F.2d at 985; *K/S HIMPP v. Hear-Wear Techs.*, LLC, 751 F.3d 1362, 1365 (Fed. Cir. 2014)(agreeing that "the Board was correct to require record

evidence to support an assertion that [claimed features] were known prior art elements."). Based on the analysis below it is clear that the combined references of Ground 2 fail to teach all elements of claim 1, and thus Petitioner fails to meet its burden of establishing the unpatentability of the claims. EX2023, ¶68.

A. Kinde 2012 Does Not Describe Normalizing a Plurality of Predefined Regions to Each Other

In addressing the quantifying step "d)" and the normalization step "e)i)", the petition argues that by "teaching generating tag counts (i.e., number of sequence reads) for each chromosomal position (i.e., regions) on the reference sequence, Kinde 2012 discloses quantifying mapped reads in a plurality of predefined regions of the reference sequence." Pet. 38-39 (citing EX1041, 4). In this step, the petition relies on the L1 retrotransposon regions as the "plurality of predefined regions." *E.g.*, EX1041, Fig. 1; EX2023, ¶69.

The petition then argues that "Kinde 2012 teaches normalizing a number of reads in a plurality of predefined regions to each other." Pet. 39. As discussed below, Kinde 2012 does not describe normalizing reads in a plurality of predefined regions to each other. This critical difference is a missing claim limitation that Petitioner attempts to sweep under the rug with conclusory and unsupported statements. The petition cites the Gabriel declaration at ¶119 for purported support, but ¶119 of the Gabriel declaration is just as conclusory and just as unsupported as the petition. That is, Gabriel ¶119 states that "By teaching normalizing the tag

counts for each position in each sample, Kinde 2012 teaches normalizing a number of reads in a plurality of predefined regions to each other." EX2023, ¶70.

Kinde 2012 describes a process of normalization that does not occur as recited in step "e)i)" claim 1, which requires "normalizing a number of reads [or unique reads] in the plurality of predefined regions to each other." Instead, Kinde 2012 normalizes reads among different samples:

> "Most importantly, the relative function of tags mapping to chromosomes was remarkably similar among the individual samples after normalizing [21] to compare chromosome tag counts among different samples."

EX1041, 6 (right column); *see also* EX2023, ¶71.

Normalizing tag counts across samples may provide information related to chromosome counts, but it does not provide any information about copy number variation in one or more of the plurality of predefined regions as recited in claim 1, step "e)i)". EX2023, ¶71. That is, the claimed process normalizes a number of reads in the plurality of predefined regions to each other. Kinde 2012 does not normalize read counts in the predefined regions to each other, and neither the petition nor Dr. Gabriel's Declaration pointed to anywhere in Kinde 2012 that this process is described. In fact, Dr. Gabriel confirmed in her deposition that Kinde 2012 normalizes across samples. EX2022, 76:7-78:17; EX2023, ¶¶71-72.

In the claimed process, by normalizing read counts of predefined regions to each other, the method maintains the focus of the claim on determining copy

number variation as that term is used throughout the '743 patent specification. The normalization process of Kinde 2012 permits comparison across patient samples. When coupled with a subsequent processing step, Kinde 2012 is said to permit determination of chromosomal aneuploidy. Contrary to the statement in the petition, however, there is nothing in Kinde 2012 of "teaching normalizing across the tag counts for each portion in each sample." Petitioner further cites to its expert, however, Dr. Gabriel is as silent on this as Kinde 2012. Pet. 39 (citing EX1002, ¶119; *see also* EX2023, ¶73. Thus, the statement in the petition appears to be a mischaracterization of Kinde 2012.

The petition goes on to assert, without basis, that "Kinde 2012 teaches processing a number of reads in a plurality of predefined regions with numbers obtained from a control sample. The 'processing' step of claim 1 refers simply to comparing the reads from the test sample to reads from a control sample." Pet. 39. The petition asserts that the method of Kinde 2012 includes calculating a "Z-score" for both test samples and control samples for a chromosome of interest. Pet. 39-40. Kinde 2012 uses this calculation to detect aneuploidy by comparing Z-scores for test samples to Z-scores for control samples. Pet. 40 (citing EX1041, Fig. 3A); *see also* EX2023, ¶74. And Dr. Gabriel confirmed in her deposition that Kinde 2012 determines aneuploidy on whole chromosomes. EX2022, 80:15-81:24 (Dr. Gabriel discussing ¶123 of her declaration, EX1002); EX2023, ¶74.

These calculations, said to be the "processing" step in claim 1, "e)ii)" (Pet. 39-41) determine aneuploidy status. EX1041, 4-5. But the predefined region being mapped in Kinde 2012 is defined by the L1 retrotransposon element. *Id.*, Fig. 1. During her deposition Dr. Gabriel confirmed that ¶115 of her declaration (EX1002) equates the L1 retrovial transposon with predefined regions. EX2022, 78:12-79:21. Step "e)ii)" specifies that the process determines copy number variation in one or more of the plurality of predefined regions. But what Kinde 2012 is said to do is determine aneuploidy of a test sample of interest when compared to other test samples, not to other predefined regions of interest as required by claim 1. EX2023, ¶75.

At bottom, in order to read Kinde 2012 on challenged claim 1, Petitioner first defines the small L1 retrotransposon elements as being the predefined region of interest, but then pivots and defines a chromosome as being a predefined region of interest for the purpose of the normalizing and processing steps. EX2023, ¶76. Such reliance on disparate disclosure of different elements that logically cannot be one and the same for different usage of the same claim element is improper and cannot satisfy Petitioner's burden of proof. EX2023, ¶76.

The petition also argues that Kinde 2011 teaches assigning unique sequence identifiers to use for DNA fragments prior to amplification and sequencing and using those to group DNA fragments into families. Pet. 41. These sequence reads

are purported to be unique sequence reads (citing EX1002, ¶24). Whether they are or not, the issue remains that there is no explanation in the petition materials as to how a POSA would use a L1 retrotransposon element as a "predefined region" in steps "d)" and "e)" of claim 1, then pivot to a purported "unique sequence read" in the normalizing and processing steps "e)1)" and "e)ii)". Nor is there any discussion of how the references would be combined. EX2023, ¶77. This argument in the petition simply highlights the fact that this aspect of Ground 2 is based entirely on hindsight, with Petitioner picking and choosing claim elements from two different references without regard how they would be combined. *Id.*

B. Neither Kinde 2012 nor Kinde 2011 Teach Determining Copy Number Variation

Neither Kinde 2011 nor Kinde 2012 provides any disclosure regarding methods for detecting copy number variation—the very subject matter of the challenged claims. As with Ground 1, Ground 2 relies on the same incorrect assumption that a "copy number variation" includes aneuploidy. EX2023, ¶78. Further, the petition never addresses how the teachings of Kinde 2011 and Kinde 2012 would or even could be combined. EX2023, ¶78.

Claim 1 requires "determining copy number variation in one or more of the plurality of predefined regions." As an initial matter, the petition does not map any disclosure for what region copy number variation is being determined. Only discussion of aneuploidy detection is provided. *E.g.*, Pet. 41 (citing EX1041,

Figure 3) ("The presence of ***aneuploidy*** (T21, T18, or T13) can be determined by comparing the z-score for the chromosome of interest in a test sample to the (normal) control samples."). The petition offers no explanation for why a POSA would understand aneuploidy detection to encompass copy number variation detection. And as discussed above, there is no reasonable basis to construe "predefined region" as encompassing a chromosome. EX2023, ¶79.

As explained above, the '743 patent specification describes aneuploidy and copy number variations as distinct genetic aberrations. *E.g.*, EX1001, 52:15-20 ("These system and methods may be used to detect any number of genetic aberrations that may cause or result from cancers. These may include but are not limited to …, ***copy number variations***, transversions, translocations, inversion, deletions, ***aneuploidy***, …") (emphasis added). The '743 patent further describes copy number variations as sub-chromosomal aberrations. *Id.*, 7:40-42 ("[T]he genetic variation is copy number/heterozygosity variation and detecting is performed with sub-chromosomal resolution."). Such a description is consistent with the requirement that "copy number variations" are determined in "predefined regions" which are much smaller than the size of a single chromosome. *Supra* Section III; *see also* EX2023, ¶80. Aneuploidies, in contrast, are genetic aberrations in the number of chromosomes. *E.g.*, EX1041, 1 ("The most common aneuploidy is trisomy 21…"); *see also* EX2023, ¶¶49-52.

Kinde 2012 does not disclose a method for detecting copy number variation as that term is defined and used in the '743 patent specification—nor does the petition assert that it does. In fact, the petition acknowledges that detecting aneuploidy is not the same as detecting "copy number variations." Pet. 34 ("[I]t also would have been obvious to a POSA to use the methods of Kinde 2011 and Kinde 2012 to detect other types of copy number variation."). The petition does not explain what is believed to constitute "other types" of copy number variations. EX2023, ¶81.

Moreover, the petition provides no explanation how Kinde 2012 should be modified to enable detection of copy number variations, much less an explanation for why a POSA would be so motivated. To the contrary, the petition argues that it "would have been obvious to a POSA to use the exact method that Kinde 2012 describes for detecting aneuploidy to detect other types of copy number variation by comparing a plurality of reads across a different group of genomic regions." Pet. 33 (citing EX1002, ¶105). What these "other types of copy number variation" might be and whether these include the claimed "copy number variations" is unexplained. EX2023, ¶82. The explanation provided in the petition falls far short of providing the required "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

C. The petition fails to establish that Kinde 2012 teaches steps (c), (d), and (e) of claim 1

The petition lumps steps (c), (d), (e), (e)(i) and (e)(ii) of claim 1 together into only a single discussion and fails to explain how the elements found in those steps are disclosed in the cited references. EX2023, ¶83. Rather than addressing the elements as they are recited in the claims, the petition reconstitutes various aspects of the claims in attempt to bootstrap its mapping based on Kinde 2012 to the claimed method. For example, the petition conflates aspects of steps (c) and (d) of claim 1, as well as steps (d) and (e)(i) of claim 1. *See* Pet. 38. As discussed above, the petition provides no discussion whatsoever for step (e) reciting "determining copy number variation in one or more of the plurality of predefined regions." *See* Pet. 37-42. As a result, the petition fails to provide an explanation of what content of Kinde 2012 is relied upon or explain how the reference discloses the identified aspects of the claims. EX2023, ¶83.

For example, the petition initially identifies "the human genome (hg19)" as the "reference sequence" recited in step (c) of claim 1. Pet. 38 (citing EX1041, 2). This assertion is inconsistent with and unsupported by the cited provision of Kinde 2012, which discloses building "the reference index" using a discrete set of chromosomal positions, noting that "[b]ecause tag alignment to a discrete set of chromosomal positions is simpler than alignment to the entire genome, the post-sequencing analysis process was very rapid." EX1041, 2; EX2023, ¶84.

In fact, after identifying the hg19 human genome as a reference sequence, the petition (38) changes tack and refers to Kinde 2012 where it explains why they did *not* map reads to the hg19 genome as a reference sequence—instead using "a discrete set of chromosomal positions" for its alignment step, which turned out to be the L1 family of retroviral transposons. Pet. 38 (quoting EX1041, 2); *see also* EX1041, Fig. 1; EX2023, ¶85.

The petition confuses the terminology of steps (c) and (d) of claim 1, concluding "[t]hus Kinde 2012 teaches mapping sequence reads to a plurality of predefined regions." Pet. 38 (referring to the "discrete set of chromosomal positions" of Kinde 2012). But, step (c) of claim 1 does not recite mapping sequence reads onto a plurality of predefined regions, rather it recites "mapping the plurality of sequence reads to a reference sequence." Step (d) of claim 1 recites, subsequent to the mapping step, "quantifying *mapped* reads or unique sequence reads in a plurality of predefined regions of the reference sequence." EX2023, ¶86.

In fact, in addressing the quantifying step (step (d)) of claim 1, the petition relies on the same "discrete set of chromosomal positions" in Kinde 2012 as providing the different claim element of "a plurality of predefined regions." Pet. 39 ("By teaching generating tag counts (i.e., number of sequence reads) for each chromosomal position (i.e., regions) on the reference sequence, Kinde 2012

teaches quantifying mapped reads in a plurality of predefined regions of the reference sequence."). EX2023, ¶87.

As a result, the petition fails to identify what is relied upon in Kinde 2012 as disclosing the "reference sequence" recited in steps c) and d) of claim 1. That is, to the extent the petition relies upon the entire hg19 human genome cited in Kinde 2012, Kinde 2012 does not map sequence reads to the hg19 genome—Kinde 2012 instead discusses "alignment to a discrete set of chromosomal positions." EX2023, ¶88.

To the extent the petition relies upon "a discrete set of chromosomal positions" as providing the claimed "reference sequence" in step (c) of claim 1, this is the same disclosure relied upon for the different claim element of "a plurality of predefined regions" in step (d) of claim 1. EX2023, ¶89. Such reliance on a single point of disclosure as providing multiple different elements of a challenged claim is improper. *Engel Indus. v. Lockformer Co.*, 96 F.3d 1398, 1405 (Fed. Cir. 1996) (concluding that where a claim provides for two separate elements, these two elements "logically cannot be one and the same"); *see also Hopkins Manufacturing Corp. v. Cequent Performance Prod., Inc.*, IPR2015-00613, Paper 9, 11-12 (determining that the claims "require that the deceleration signal and the inclination signal are separate and distinct" and thus cannot be anticipated by a single prior art structure).

With respect to the discussion of elements (d) and (e)(i), the petition merely quotes disclosure of the "quantile normalization" procedure and concludes without further support that Kinde 2012 teaches each of these elements. Pet. 39 (quoting EX1041, 4); *e.g., id.* ("By teaching generating tag counts (i.e., number of sequence reads) for each chromosomal position (i.e., regions) on the reference sequence, Kinde 2012 teaches quantifying mapped reads in a plurality of predefined regions of the reference sequence."). Merely asserting that these elements are taught by Kinde 2012, with nothing more, is insufficient to prove obviousness. As the Federal Circuit explained, "[s]imply stating that [the prior art] discloses [the claim element] does not satisfy [petitioner's] burden" to "show with particularity why the [claim] it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363-64 (Fed. Cir. 2016). EX2023, ¶90.

Accordingly, the petition fails to establish that steps (c), (d) and (e) are found in the cited references. The petition fails to prove that Kinde 2012 discloses "mapping the plurality of sequence reads to a ***reference sequence***" and "quantifying mapped reads … in a ***plurality of predefined regions*** of the reference sequence." EX2023, ¶91.

D. Motivation to combine and reasonable expectation of success are unexplained

The petition fails to explain why a POSA would have combined Kinde 2012 with Kinde 2011, and fails to establish that there was a reasonable expectation of

success for the combination specifically proposed. Although there is a section titled "Motivation to Combine and Reasonable Expectation of Success" (Pet. 31-34), the argument in this section is disconnected from the actual combination of Kinde 2012 and Kinde 2011 as applied in the petition's claim mapping exercise. *See, e.g.*, Pet. 34-42; EX2023, ¶92.

For example, the petition relies on the method of Kinde 2012 for each of claim 1 steps (a), (c), (d), and (e). Pet. 34-35, 37-42. For step (b) of claim 1, the petition relies only on Kinde 2011 as providing disclosure of a sequence read filtering technique. Pet. 36. But the petition is silent as to why a POSA would be motivated to employ this filtering technique of Kinde 2011 in the method of Kinde 2012. *See e.g.*, Pet. 31-34; EX2023, ¶93.

The petition proposes using "the library preparation and sequencing techniques taught by Kinde 2011 with the methods of analysis taught by Kinde 2012." Pet. 33. But the petition does not explain how or why the sequence read filtering technique of Kinde 2011 is better substituted as a "library preparation" or "sequencing" technique, rather than as a post-sequencing analytic step as it is disclosed and used in Kinde 2011. EX2023, ¶94.

The petition asserts that "[t]he method of Kinde 2012 incorporates the method of Kinde 2011." Pet. 32. But as Petitioner acknowledges, Kinde 2011 discloses multiple distinct embodiments. *See, e.g.*, IPR2019-00653, Pet. 41

("Kinde describes various embodiments of its approach."). Kinde 2012 does not describe using a Safe-SeqS embodiment as used in Kinde 2011, but rather describes a different method, which it calls FAST-SeqS. The petition does not explain which Kinde 2011 library preparation embodiment (*i.e.*, endogenous UID method or exogenous UID method) it relies on. Moreover, while the petition asserts that templates were amplified in Kinde 2012 in a manner similar to Kinde 2011, no explanation is provided how the sequence read filtering technique of Kinde 2011 are to be used as either a "library preparation" or "sequencing" technique, rather than a post-sequencing analytic step as taught in Kinde 2011. *See* Pet. 32.

With respect to certain dependent claims (e.g. claims 3-7 and 9), it should first be noted that these claims are not unpatentable because they depend, either directly or indirectly, from claim 1, which has been shown to be not unpatentable based on the assertions in Ground 2 of petition. Dr. John Quackenbush is an expert who is well qualified in the field to address the references as applied to these claims from the perspective of a POSA. EX2026, ¶¶21-24. His expert declaration is provided as EX2026, and his *Curriculum Vitae* is EX2027.

Dr. Quackenbush has reviewed the petition materials and supporting exhibits and it is his opinion that dependent claims 3-7 and 9 are patentable over the combination of Kinde 2011 and Kinde 2012. EX2026, ¶¶25-26. As an initial

matter, Dr. Quackenbush first notes that the petition relies on the method of Kinde 2012 for each of claim 1 steps (a), (c), (d), and (e) (citing Pet. 34-35, 37-42), yet, for its analysis of dependent claims 3-7, and 9, the petition refers only to Kinde 2011. EX2026, ¶27. Moreover, he notes that the petition does not explain how the teachings of Kinde 2011 and Kinde 2012 would have been combined, or even whether they could be combined, at least in the context of these dependent claims. *Id.*

Regarding claim 3, the petition asserts that "Kinde 2011 teaches making copies of the DNA fragments through an amplification step prior to sequencing." Pet. 42. But this statement does not address the claimed subject matter because it does not explain how Kinde 2011 teaches or suggests generating copies of the extracellular polynucleotides prior to sequencing, as expressly recited in claim 3. EX2026, ¶28.

The petitions failure to address the limitations of claim 3 is unsurprising—Kinde 2011 deals exclusively with cellular DNA samples. EX2026, ¶29, referring to Kinde 2011 (EX1023) at, e.g., 9530 (Abstract), 9531, 9533, and SI1. It is Dr. Quackenbush's opinion that Kinde 2011's methods are inapplicable to extracellular polynucleotides, and the failure of the petition to address this limitation in claim 3 highlights the differences between the claim and what the combined references actually teach. EX2026, ¶¶29, 30.

With respect to claim 4, Dr. Quackenbush notes that the petition does not explain why a POSA would have made a calculation of the percent of sequences having a rare mutation, or how even such a calculation would have been made using the technique of Kinde 2012 that was relied on for carrying out the method of claim 1. EX2026, ¶31.

Moreover, while the petition argues in regard to claim 4 that the art shows a "rare mutation", Kinde 2012 does not disclose detecting a "rare mutation" or any other type of mutation. Instead, Kinde 2012 describes a method for determining aneuploidy through detection of an excess of sequence reads associated with a particular chromosome. EX2026, ¶32. Thus, this element of claim 4 is missing from the reference that is relied upon.

Each of dependent claims 5-7, and 9 require barcodes that are attached to extracellular polynucleotides. But the references relied on in the petition materials deal exclusively with analyzing cellular DNA—not extracellular polynucleotides. EX2026, ¶33. Thus, the references say nothing about attaching barcodes to extracellular polynucleotides. *Id.* Dr. Quackenbush notes that there are substantial differences between labeling abundant cellular DNA and labeling low-abundance, low-concentration extracellular polynucleotides. *Id.* There is no evidence in the petition materials that a POSA would consider using the "bulk DNA" methods of

the references for the purposes envisioned in the '743 patent or the use as recited in these dependent claims.

For example, each of dependent claims 5-7, and 9 require that the attachment occur between the barcodes and extracellular polynucleotides. As recited in independent claim 1, the extracellular polynucleotides are "from a bodily sample from a subject." But instead of barcoding extracellular polynucleotides from a subject as recited in these claims, Kinde 2011 instead incorporates indexed primers through PCR amplification. EX2026, ¶34. That is, Kinde 2011 tags amplification progeny—not polynucleotides from a subject which is recited in the claim. It is clear that Kinde 2011 does not disclose or suggest this limitation found in claims 5-7 and 9.

Furthermore, dependent claims 6 and 7 require attaching non-unique barcodes to the extracellular polynucleotides. The petition materials rely on an endogenous UID embodiment of Kinde 2011 as allegedly disclosing "barcodes that are not unique." Pet. 47; EX2026, ¶35 (Pet. 46 (quoting EX1023, SI1, 9531)). That is, the petition relies on an embodiment that uses sheared ends of polynucleotides as UIDs. EX2026, ¶35.

However, as Dr. Quackenbush explains in his declaration, the petition relies on Kinde 2012 as "teach[ing] amplifying extracellular polynucleotides (i.e., cell-free DNA) from a bodily sample of maternal plasma, to create copies of each

polynucleotide, and sequencing the copies, thereby generating a plurality of sequence reads for each polynucleotide." Pet. 34 (citing EX1041, Abstract, 2). According to Dr. Quackenbush, fragments that are amplified by PCR do not have sheared ends, and because the extracellular polynucleotides of Kinde 2012 are amplified with "a single primer pair" all amplicons have the same terminal sequences (i.e., the primer sequences). That is, the method of Kinde 2012 does not produce the sheared ends required by the endogenous UID embodiment of Kinde 2011. EX2026, ¶36.

With respect to claim 7 the petition concludes that "[a] POSA thus would have understood DNA fragments with sheared ends to be 'a diversity of molecules' within the meaning of claim 7." Pet. 50. But again, the method of Kinde 2012 does not produce sheared ends. In fact, all amplicons have identical terminal sequences. EX2026, ¶37. Thus, the combined references are missing this element of claim 7 upon which the petition relies.

The petition fails to explain how the various embodiments of Kinde 2012 and Kinde 2011 are to be combined, much less why, and fails to explain the absence of several limitations of the claims from the references. Without such explanations, it follows that there no cannot be a reasonable expectation of success. Given these deficiencies stemming from a lack of explanation in the petition

materials as well as the references themselves, even a *prima facie* case of obviousness as to claims 1-9, 20 and 22-26 as asserted in Ground 2 fails.

VI. RESPONSE TO GROUND 3

The Board has already determined that the petition did not demonstrate a reasonable likelihood of success in showing that claims challenged in Ground 3 are obvious over Kinde 2011 combined with Forshew. Paper 10, 31. Agreeing with Patent Owner, the Board found that nothing in Kinde 2011 or Forshew teaches the use of unique identifiers or barcodes to identify the fragments. EX2023, ¶97.

Thus, as with Grounds 1 and 2, Ground 3 fails to demonstrate that the cited references disclose all elements of the challenged claims. For example, Forshew does not disclose "unique sequence reads," as is required by step (f) of claim 10. Furthermore, the petition fails to establish that the method of Kinde 2011 is applicable to cell-free DNA molecules.

A. Missing element -- "unique sequence read" -- step (f) of claim 10

Step (f) of claim 10 requires "calculating a ratio of (a) a number of mapped ***unique sequence reads*** that include a variant as compared to the reference sequence, to (b) a number of total ***unique sequence reads*** for each mappable base position." EX1001, claim 10. The petition materials fail to identify any prior art teachings of this element. *E.g.*, Pet. 61 ("Accordingly, a POSA would have understood Forshew, by teaching calculating the allele frequency, to teach

"calculating a ratio of mapped ***sequence reads*** that include a variant as compared to the reference sequence to a number of ***total sequence reads***."), 62 ("A POSA would have understood this table to depict mappable base positions, where ***sequence reads*** mapping to the positions may contain mutations. EX1002, ¶204."), 63 ("Accordingly, Forshew teaches calculating a ratio of mapped ***reads*** that include a variant to the total number of mapped ***reads*** (i.e., the allele frequency) for each of multiple mappable base positions."). EX2023, ¶98.

Forshew does not disclose "unique sequence reads" nor does the petition allege that it does. Ground 3 is legally and factually insufficient to make out a case of prima facie obviousness or even a reasonable likelihood that the claims would have been obvious. EX2023, ¶98.

B. No motivation to combine Kinde 2011 and Forshew

The argument in the petition materials of a "motivation to combine" Forshew and Kinde 2011 (Pet. 53-54) largely revolves around an assertion that both references utilize a similar class of sequencing technology. *See e.g.*, Pet. 54 ("A POSA would have been motivated to combine the methods of Forshew and Kinde 2011 because both references teach the use of similar technology (i.e., next generation sequencing technology) to detect rare mutations."). EX2023, ¶99.

Merely identifying one similarity in what are otherwise divergent methods does not complete the obviousness inquiry. In particular, obviousness requires an

articulated rationale with logical underpinnings. *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *W.L. Gore & Associates, Inc. v. Garloc, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983) ("[T]he district court erred … in considering the [prior art] references in less than their entireties…."); *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1379 (Fed. Cir. 2016) (merely "noting surface similarities between the [asserted] references" is insufficient to demonstrates motivation to combine; "[t]hese surface similarities do not control the obviousness analysis because they are not directed to the relevant features of the claimed invention").

No such rationale is provided in the petition materials. At best, the arguments merely identify surface similarities between Forshew and Kinde 2011 that have no pertinence to the subject matter claimed in the '743 patent. *E.g.*, *Magnum Oil Tools*, 829 F.3d at 1379; *Securus Technologies, Inc., v. Global Tel*Link Corp.*, IPR2015-00155, Paper 30 at 18 ("The cursory assertion that the prior-art references are drawn from the same broadly characterized field provides insufficient analysis concerning why and how a POSA would have modified or combined the prior art in the manner asserted, and inadequately articulates 'reasoning with some rational underpinning to support the legal conclusion of obviousness.'") (quoting *KSR*, 550 U.S. at 418); *Agilent Technologies, Inc., v. Bio-Rad Laboratories, Inc.*, Case IPR2019-00266, Paper 8, 23-24 (similar); EX2023, ¶99.

Beyond that, Kinde 2011 only discusses analysis of cellular DNA, and does not provide a description of applying to cell-free DNA as that term is properly construed in the '743 patent specification. The assertion that Kinde 2011 describes a method to address "'clinical samples wherein the mutation prevalence can be ≤0.01%,' which was a mutation frequency that was known to be likely to occur in cell-free DNA" (Pet. 54) merely explains that mutations of interest were known in the art to be present at low levels in clinical samples. EX1023, 9530. This citation does not amount to disclosure of application of Kinde 2011 to cell-free DNA. EX2023, ¶100.

Moreover, an argument for detecting low-prevalence mutation does not address whether Kinde 2011 would be used or expected to successfully detect mutations in a fundamentally different type of sample—*i.e.*, cell-free DNA. This is critically important, though unaddressed, as it was well-known that cell-free DNA presented unique technical difficulties compared to analysis of cellular DNA and required specialized methods. EX2003, 3. Yet the petition materials omit any discussion dealing with the drawbacks involving cell-free DNA compared to cellular DNA samples. EX2023, ¶101.

C. How the references are combined is unaddressed

Petitioner bears an unshifting burden of proving unpatentability of the challenged claims. *Magnum Oil Tools*, 829 F.3d at 1376. Obviousness requires,

inter alia, rationale or motivation to make the modification being proposed, explanation as to how a POSA would go about combining the references, and a reasonable expectation of success. *In re NuVasive, Inc.*, 842 F.3d 1376, 1382 (Fed. Cir. 2016); *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017); *In re Stepan Co.*, 868 F.3d 1342, 1346 n.1 (Fed. Cir. 2017). Here, the petition materials fail to provide an explanation how to combine the teachings of Kinde 2011 and Forshew to reach the claimed invention. EX2023, ¶102.

The petition proposes a combination of the Kinde 2011 method with the cell-free DNA samples of Forshew. However, in mapping the elements of claim 10, Petitioner relies exclusively on Forshew for elements (f) and (g) which recite:

> f) for each mappable base position, calculating a ratio of (a) a number of mapped unique sequence reads that include a variant as compared to the reference sequence, to (b) a number of total unique sequence reads for each mappable base position; and
> g) processing the ratio with a similarly derived number from a reference sample.

The petition does not address how the aspects of Forshew's method that allegedly disclose elements (f) and (g) of claim 10 could or would be combined with the method of Kinde 2011. Lacking such explanation, one is left to surmise what might have been intended about how to combine the teachings of the references. This is not only a failure to prove obviousness, but also a blatant failure to comply with

the statutory requirement that challenges be made with "particularity." *See* 35 U.S.C. § 312(a)(3). EX2023, ¶102.

VII. RESPONSE TO GROUND 4

The Board has already determined that Ground 4 lacks a reasonable likelihood of success. Paper 10, 33. Ground 4 alleges that dependent claim 14 is obvious over Kinde 2011, Kinde 2012, and Forshew. The petition fails to prove a reasonable likelihood of success in Ground 3 as to claim 10. Claim 14 depends from claim 10, thus claim 14 is not unpatentable for the same reasons that claim 10 is not unpatentable. EX2023, ¶103.

Moreover, the petition merely quotes disclosure found in Kinde 2012 regarding the calculation of z-scores for chromosomes, without any discussion as to why such disclosure reads on the claimed "calculating a percent of predefined regions with an amount of polynucleotides above or below a threshold." Pet. 70. Merely asserting that this element is taught by Kinde 2012, with nothing more, is insufficient to prove obviousness. *Harmonic Inc.*, 815 F.3d at 1363-64. EX2023, ¶104.

Accordingly, there is no basis on which to conclude that claim 14 is unpatentable over Kinde 2011, Kinde 2012, and Forshew. EX2023, ¶105.

VIII. CONCLUSION

Accordingly, for at least the reasons set forth above, Petitioner has not met its burden of proving the claims are unpatentable by a preponderance of the evidence.

Respectfully submitted,

Date: December 4, 2019

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
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CERTIFICATE OF COMPLIANCE

Pursuant to §42.24(d), the undersigned certifies that this paper contains no more than 11,566 words, not including the portions of the paper exempted by §42.24(b). According to the word-processing system used to prepare this paper, the paper contains 11,033 words.

Respectfully submitted,

Date: December 4, 2019

/ Michael T. Rosato /
Michael T. Rosato, Lead Counsel
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IX. APPENDIX

Exhibit No.	Description
2001	Intentionally Left Blank
2002	Intentionally Left Blank
2003	Niall J. Lennon, Viktor A. Adalsteinsson and Stacey B. Gabriel, "Technological considerations for genome-guided diagnosis and management of cancer," Genome Medicine (2016) 8:112
2004	Intentionally Left Blank
2005	Guardant Health, Inc. v. Personal Genome Diagnostics, Inc., Case No. 17-cv-1623, Document 10, First Amended Complaint, filed February 5, 2018
2006	Guardant Health, Inc. v. Foundation Medicine, Inc., Case No. 17-cv-1616, Document 10, First Amended Complaint, filed February 5, 2018
2007	Guardant Health, Inc. v. Foundation Medicine, Inc., Case No. 17-cv-1616 and Guardant Health, Inc. v. Personal Genome Diagnostics, Inc., Case No. 17-cv-1623, Scheduling Conference Transcript, March 26, 2018
2008	Guardant Health, Inc. v. Foundation Medicine, Inc., Case No. 17-cv-1616, Document 20, Defendant Foundation Medicine, Inc.'s Answer to Plaintiff's Second Amended Complaint and Counterclaims, filed March 26, 2018
2009	Guardant Health, Inc. v. Foundation Medicine, Inc., Case No. 17-cv-1616, Defendant's Initial invalidity Contentions, filed June 25, 2018

Exhibit No.	Description
2010	Guardant Health, Inc. v. Foundation Medicine, Inc., Case No. 17-cv-1616 and Guardant Health, Inc. v. Personal Genome Diagnostics, Inc., Case No. 17-cv-1623, Scheduling Order, filed April 4, 2018
2011-2013	Intentionally Left Blank
2014	U.S. Pat. Appl. No. 15/811,836, January 9, 2019 Office Action Response
2015	Guardant Health, Inc. v. Personal Genome Diagnostics, Inc., Case. No. 17-cv-1623, REDACTED Transcript of Deposition of Victor Velculescu, April 19, 2019
2016	Guardant Health, Inc. v. Personal Genome Diagnostics, Inc., Case. No. 17-cv-1623, REDACTED Transcript of Deposition of Mark Sausen, March 27, 2019
2017	Decision issued January 15, 2019 in Japanese Opposition 2018-700659
2018	Intentionally Left Blank
2019	Transcript of June 12, 2019 Conference Call
2020	Guardant Health, Inc. v. Foundation Medicine, Inc., case No. 17-cv-1616 (LPS)(CJB), REDACTED Expert Report of Stacey Gabriel, Ph.D. regarding Invalidity, July 24, 2019
2021	Guardant Health, Inc. v. Foundation Medicine, Inc., Case No. 17-cv-1616 (LPS)(CJB), Transcript of Deposition of Stacey Gabriel, Ph.D., October 24, 2019
2022	Guardant Health, Inc. v. Foundation Medicine, Inc., IPR2019-00634, -00652, Transcript of Deposition of Stacey Gabriel, Ph.D., November 5, 2019

Exhibit No.	Description
2023	Declaration of Carlos D. Bustamante, Ph.D.
2024	Declaration of Carlos D. Bustamante, Ph.D. in Support of Patent Owner's contingent Motion to Amend
2025	Curriculum Vitae of Carlos D. Bustamante, Ph.D.
2026	Declaration of Dr. John Quackenbush
2027	Curriculum Vitae of Dr. John Quackenbush
2028	AmirAli Talasaz, "System and Methods to Detect Rare Mutations and Copy a Number Variation," U.S. Pat. Appl. No. 15/467,570, March 23, 2017
2029	AmirAli Talasaz, "System and Methods to Detect Rare Mutations and Copy a Number Variation," U.S. Pat. Appl. No. 14/425,189, March 2, 2015
2030	AmirAli Talasaz, "System and Methods to Detect Rare Mutations and Copy a Number Variation," PCT Application No. PCT/US2013/058061, September 4, 2013
2031	AmirAli Talasaz et al., "System and Methods to Detect Rare Mutations and Copy a Number Variation," U.S. Provisional Pat. Appl. No. 61/845,987, July 13, 2013
2032	AmirAli Talasaz, "System and Methods to Detect Rare Mutations and Copy a Number Variation," U.S. Provisional Pat. Appl. No. 61/793,997, March 15, 2013
2033	AmirAli Talasaz, "System and Methods to Detect Rare Mutations and Copy a Number Variation," U.S. Provisional Pat. Appl. No. 61/704,400, September 21, 2012

Exhibit No.	Description
2034	AmirAli Talasaz, "System and Methods to Detect Rare Mutations and Copy a Number Variation," U.S. Provisional Pat. Appl. No. 61/696,734, September 4, 2012
2035	Help – CNV Overview Page, https://cancer.sanger.ac.uk/cosmic/help/cnv/overview (last access December 3, 2019)
2036	Peter Van Loo et al., *Allele-specific copy number analysis of tumors*, PNAS 107(39) (September 28, 2010)

CERTIFICATE OF SERVICE

I certify that the foregoing Patent Owner's Response Pursuant to 37 C.F.R. § 42.120 and accompanying Exhibits 2020-2036 were served on this 4th day of December, 2019, on the Petitioner at the following electronic service addresses:

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