UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,584,968 B2
APPLICATION NO. : 17/494513
DATED : February 21, 2023
INVENTOR(S) : John West

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Claim 11, Column 55, Lines 37-38, change "multiple nucleotide polymorphisms (HNPs)" to -- multiple nucleotide polymorphisms (MNPs) --.

Claim 16, Column 56, Lines 38-39, delete "from a source or".

Claim 20, Column 56, Lines 57-58, change "multiple nucleotide polymorphisms (HNPs)" to -- multiple nucleotide polymorphisms (MNPs) --.

Signed and Sealed this
Twenty-fifth Day of April, 2023

Katherine Kelly Vidal

Katherine Kelly Vidal
Director of the United States Patent and Trademark Office

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/494,513	**03/27/2023 02:38:21 PM ET**	**48929.4008/US03**

Title of Invention

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	11584968
CONFIRMATION #	8186	FILED BY	Sheila Gloss
PATENT CENTER #	61810643	FILING DATE	10/05/2021
CUSTOMER #	182685	FIRST NAMED INVENTOR	John West
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Alex Straughn

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
48929_4008US03_sb0044.pdf	2	Request for Certificate of Correction	171 KB
48929_4008US03_Transmittal_CoC.pdf	16	Request for Certificate of Correction	919 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
48929_4008US03_sb0044.pdf	4DFCE6DA06F10175F981DD99F295BA8B00AE63D7FD3517734 68FFF5C2B221D5EA252FAD240265458C408DD40A391B08105

	B0346E68B1F7E70E48D45879D1F1A0
48929_4008US03_Transmittal_CoC.pdf	C2DD3ED14CC62B6A6B8BEABF397A8F23789825BB6888C92710A02A55FBE147E5DDE01D178431E5B1D2CC202B9273D6FAA2638E56EA8E86DF0CE05D9CD831A32C

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

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

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

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

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

PTO/SB/44 (09-07)
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 11,584,968

APPLICATION NO.: 17/494,513

ISSUE DATE : 02-21-2023

INVENTOR(S) : John West

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 11, Column 55, Lines 37-38, change “multiple nucleotide polymorphisms (HNPs)” to -- multiple nucleotide polymorphisms (MNPs) --.

Claim 16, Column 56, Lines 38-39, delete "from a source or".

Claim 20, Column 56, Lines 57-58, change “multiple nucleotide polymorphisms (HNPs)” to -- multiple nucleotide polymorphisms (MNPs) --.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):

ORRICK, HERRINGTON & SUTCLIFFE LLP
2050 Main Street, Suite 1100
IRVINE, CA 92614

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. 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 1.0 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: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: **John West**	Examiner: **Joseph T Woitach**
U.S. Serial No.: **17/494,513**	Art Unit: **1672**
Filing Date: **October 5, 2021**	Confirmation No.: **8186**
For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Attorney Docket: **48929.4008/US03** Patent No. **11,584,968** Issued: **February 21, 2023**

Via Patent Center
Commissioner for Patents
Office of Data Management
Attention: Certificates of Correction Branch
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT
FOR PTO MISTAKE (37 CFR 1.322(a))

Dear Sir:

Attached is Form PTO/SB/44 – Certificate of Correction.

1. On page 40 of the Letters Patent of the above-referenced patent, applicant respectfully requests the following corrections:

Claim 11, Column 55, Lines 37-38, change "multiple nucleotide polymorphisms (HNPs)" to -- multiple nucleotide polymorphisms (MNPs) --.

Claim 16, Column 56, Lines 38-39, delete "from a source or".

Claim 20. Column 56, Lines 57-58, change "multiple nucleotide polymorphisms (HNPs)" to -- multiple nucleotide polymorphisms (MNPs) --.

2. The above-referenced corrections relate to mistakes in the granted patent incurred through the fault of the Office. Please see the amended claims submitted to the Office in the Response to Non-Final Office Action filed November 11, 2022 (copy attached). The claims submitted in the November 11, 2022 were allowed December 15, 2022.

3. Fee and Method of Fee Payment for Certificate of Correction:

☒ To our knowledge, no fees are required.

☐ Attached is a check for _____.

☐ Charge Account 15-0665 ($_____).

☒ If any additional fees are due, please charge Account 15-0665.

4. Please forward the Certificate to the undersigned.

Respectfully submitted,

ORRICK, HERRINGTON & SUTCLIFFE LLI

Dated: March 27, 2023

/Alex Straughn/

Alex Straughn, Reg. No. 80,155
for Gargi Talukder, Reg. No. 61,368

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Tel: 949-567-6700
Fax: 949-567-6710
Customer Number: 34313

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1672
PERSONALIS, INC.	Examiner: Joseph T. Woitach
Serial No.: 17/494,513	Customer No. 182685
Filed: October 5, 2021	Confirmation No. 8186
For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Attorney Docket No. 48929.4008/US03

Filed via Patent Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

Commissioner:

This communication is responsive to the Non-final Office Action of August 29, 2022. This response is being filed on or by November 29, 2022, making it a timely filed response.

Amendments to the Claims begin on page 2 of this paper; and

Remarks begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listing of claims in the application.

1-9. (Canceled)

10. (Currently amended) A method of analyzing a biological sample obtained from a subject being screened for a cancer, wherein the biological sample is from a non-fetal source, the method comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, and wherein (i) said first set of nucleic acid molecules is extracted from tissue sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a blood sample;

(b) using said first set of sequence reads and said second set of sequence reads to identify ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(c) subsequent to (b), identifying said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in a first additional sample of said subject, wherein said first additional sample is obtained from a source that is different than said tissue sample and at a time point that is different than said tissue sample; and

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(d) providing a report based on an identification of said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said subject.

11. (Currently amended) The method of claim 10, further comprising identifying ~~one or more second~~ mosaic variants specific to said tissue sample of said subject in a second additional sample of said subject, wherein said second additional sample comprises cell-free DNA, which second additional sample is obtained ~~from a source or~~ at a time point that is different than said tissue sample and said first additional sample.

12. (Currently amended) The method of claim 10, further comprising providing a recommendation for a therapeutic intervention based on an identification of said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject.

13. (Previously presented) The method of claim 10, wherein said tissue sample comprises a metastatic tissue sample, a mixed tissue sample, a biopsy, or a core needle biopsy.

14. (Previously presented) The method of claim 11, wherein said first and/or second additional sample comprises a blood sample, a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.

15. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

16. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are causal or predisposing for a cancer.

17. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are non-causal for a cancer.

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18. (Currently amended) The method of claim ~~11~~ 10, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, or first additional sample~~, or second additional sample~~.

19. (Previously presented) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, first additional sample, or second additional sample.

20. (Currently amended) A method for early disease detection in a subject using at least two samples from the subject, wherein the at least two samples are from a non-fetal source, said method comprising:

(a) obtaining a blood sample from said subject;

(b) extracting (i) a first set of nucleic acid molecules from a first component separated from a blood sample of said subject and (ii) a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample;

(c) quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules present in said first component separated from a blood sample;

(d) comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity;

(e) if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads generated by sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules;

(f) using said first set of sequence reads and said second set of sequence reads to identify ~~one or more first~~ mosaic variants specific to said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(g) subsequent to (f), identifying said ~~one or more first~~ mosaic variants specific to said subject in a second sample of said subject, which second sample is obtained ~~from a source or~~ at a time point that is different than said blood sample; and

(h) providing a report based on an identification of said ~~one or more first~~ mosaic variants specific to said subject in said second sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in said subject.

21. (Previously presented) The method of claim 20, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

22. (Currently amended) The method of claim 20, further comprising identifying ~~one or more second~~ mosaic variants specific to said subject in a third sample of said subject, which third sample is obtained ~~from a source or~~ at a time point that is different than said blood sample and said second sample.

23. (Currently amended) The method of claim 22, wherein said second or third sample comprises a blood sample, ~~a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy,~~ a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.

24. (Currently amended) The method of claim 20, further comprising providing a recommendation for a therapeutic intervention based on an identification of said ~~one or more first~~ mosaic variants specific to said subject.

25. (Currently amended) The method of claim 22 wherein said ~~one or more first and/or second~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

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26. (Currently amended) The method of claim 10, wherein said ~~one or more first~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

27. (Currently amended) The method of claim 20, wherein said ~~one or more first~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

28. (Previously presented) The method of claim 10, wherein said predicting, diagnosing, and/or prognosing of (d) comprises one or more of the following: (i) diagnosing a cancer, (ii) identifying a cancer, (iii) determining a stage of a cancer, (iv) assessing risk of a cancer, (v) assessing risk of cancer recurrence, (vi) assessing reproductive risk, (vii) assessing efficacy of a drug, (viii) assessing risk of an adverse drug reaction, (ix) predicting optimal drug dosage, (x) predicting drug resistance, or any combination thereof.

29. (New) The method of claim 10, wherein said mosaic variants specific to said tissue sample of said subject are identified using capture probes in said first additional sample of step (c).

30. (New) The method of claim 20, wherein said mosaic variants specific to said subject are identified using capture probes in said second sample of step (g).

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REMARKS

A. Status of the claims

Claims 10-28 are currently pending in the application. With this amendment, claims 10-12, 15-18, 20, and 22-27 have been amended, and new claims 29 and 30 are added. These amendments are fully supported throughout the specification, including at, for example, paragraphs [0041], [0070], [0076], [0117], [0130], and [0170-0172]. Applicant respectfully requests entry of the claims as amended.

B. Applicant-Initiated Interview Summaries

Applicant would like to thank Examiner Woitach for the opportunity to have a first interview on September 29, 2022, as well as a second interview on November 2, 2022, to discuss the pending application. In accordance with MPEP § 713.04, Applicant provides below summaries of the substance of the interviews.

1. Interview on September 29, 2022

During the first interview, the pending rejections and potential amendments to the claims to overcome the pending rejections were discussed. In addition, with respect to the 35 U.S.C. 101 rejection, possible elements that would be considered under Step 2B as being unconventional were discussed, as were how the combination of steps provides for an integration and significantly more. The Examiner noted that the proposed amendments to the claims were likely to overcome the 112 rejections and the Examiner kindly agreed to review further potential amendments prior to Applicant filing the next response.

2. Interview on November 2, 2022

During the second interview, further potential amendments to the claims were discussed. The Examiner noted that the proposed amendments to the claims had the potential to overcome the remaining rejections pending additional review and searching.

Applicant would like to again thank the Examiner for his time, as well as for consideration of the proposed amendments and supporting arguments thereof.

C. Double Patenting

Claims 10-28 are rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of co-pending Application No. 17/828,572 filed 5/31/2022 (restriction mailed 7/25/2022).

For the purposes of expediting prosecution of the present application, Applicant files herewith a Terminal Disclaimer and respectfully submits that the Office's non-statutory double patenting rejection of claims 10-28 are moot and should be withdrawn.

D. Rejection under 35 U.S.C. § 112(a)

The Office has rejected claims 10-28 under 35 U.S.C. §112(a) as allegedly failing to comply with the written description requirement. Applicant respectfully disagrees.

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended claims 10 and 11 to clarify certain elements of the claims, as suggested by the Office (see, e.g., page 7 of the most recent Office Action). Applicant submits that, in view of the amendments to claims 10 and 11, a person of ordinary skill in the art would readily understand and appreciate the elements of the claims upon review of the specification as a whole.

In view of the foregoing, Applicant respectfully submits that claims 10-28 are in compliance with 35 U.S.C. §112(a). As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112(a) be withdrawn.

E. Rejection under 35 U.S.C. § 112(b)

The Office has rejected claims 10-28 under 35 U.S.C. §112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor regards as the invention. Applicant respectfully disagrees.

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended claims 10 and 11 to clarify certain elements of the claims, as suggested by the Office (see, e.g., page 8 of the most recent Office Action). Applicant

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submits that, in view of the amendments to claims 10 and 11, the claims are not indefinite as there is no longer ambiguity as to what "different" is in reference to when the claims are read in their entirety.

In view of the foregoing, Applicant respectfully submits that claims 10-28 are in compliance with 35 U.S.C. §112(b). As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112(b) be withdrawn.

F. Rejection under 35 U.S.C. § 103

The Office maintains its rejection of claims 10-25 and rejects newly added claims 26-28 under 35 U.S.C. 103 as allegedly being unpatentable over Lo et al. (1997) ("Lo"), Benesova et al. (2013) ("Benesova"), De Mattos-Arruda et al. (2013) ("De Mattos-Arruda"), Laktionov et al. (2004) ("Laktionov"), Ellinger et al. (Urologic Oncology 29:124-129 (2011)) ("Ellinger"), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)) ("Jung"), Shaw et al. (Genome Research 22:220-231 (2012)) ("Shaw"), Lewis et al. (US 2012/0058480 Al) ("Lewis"), and Green et al. (US 2005/0260645 Al) ("Green").

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended independent claims 10 and 20 to clarify certain differences over the asserted combination of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green. Applicant submits that the claims as amended are not obvious in view of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green, because none of the references, alone or in combination, teaches or discloses all of the elements of independent claims 10 and 20.

For example, nothing in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green teaches or discloses, or even suggests, "A method of analyzing a biological sample obtained from a subject being screened for a cancer…wherein **[the] first set of sequence reads and [the] second set of sequences reads are generated using whole genome sequencing**, …**using [the] first set of sequence reads and [the] second set of sequence reads to identify mosaic variants specific to [the] tissue sample in [the] first set of sequence reads that is not present in [the] second set of sequence reads**…**identifying [the] mosaic variants specific to [the] tissue sample of [the] subject in a first additional sample of [the] subject**…

and…**providing a report based on an identification of [the] mosaic variants specific to [the] tissue sample of [the] subject in [the] first additional sample**…," as recited in claim 10 (emphasis added).

Further, nothing in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green teaches or discloses, or even suggests, "A method for early disease detection in a subject using at least two samples from the subject…wherein **[the] first set of sequence reads and [the] second set of sequence reads are generated using whole genome sequencing**…**using [the] first set of sequence reads and [the] second set of sequence reads to identify mosaic variants specific to [the] subject in [the] first set of sequence reads that is not present in [the] second set of sequence reads**…**identifying [the] mosaic variants specific to [the] subject in a second sample of [the] subject**…and…**providing a report based on an identification of [the] mosaic variants specific to [the] subject in [the] second sample**…," as recited in claim 20 (emphasis added).

In addition to the above references not disclosing all elements of the claims, the claimed invention has unexpectedly superior properties when compared to Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green. For example, the methods of the claimed invention perform a comparative analysis of the first set of sequence reads and the second set of sequence reads to identify mosaic variants that are specific to the tissue sample (claim 10) or the individual (claim 20), whereas the references cited in the Office Action merely assay a sample using a predefined panel of mutations that are agnostic to the subject being screened. As such, the claimed methods exhibit technical superiority over the cited references at least for the reason that the claimed methods have a higher sensitivity for the detection of mosaic variants (see, e.g., paragraph [0066] of the specification, as well as the exhibits that were submitted as part of the email correspondence with the Office on October 24, 2022, in conjunction with the interviews with the Examiner), facilitating an earlier detection of disease, such as, for example, cancer. The references cited in the Office Action do not contemplate performing such a comparative analysis due to the simple fact that those references are only concerned with detecting common mutations that are broadly applicable to the human population at large, resulting in a concomitant decrease in assay sensitivity.

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Further, as opposed to the methods discussed in the cited references, the claimed methods are not restricted to the identification of cancer driver genes. As discussed in claims 16 and 17, the methods of the claims allow for the detection of mosaic variants that are causal or predisposing of cancer, as well as mosaic variants that are not causal for cancer. While it is now more commonly known that mosaic variants are present in normal tissue (*see, e.g., Muyas, F., Zapata, L., Guigó, R., & Ossowski, S. (2020). The rate and spectrum of mosaic mutations during embryogenesis revealed by RNA sequencing of 49 tissues. Genome Medicine, 12(1).*), Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green failed to disclose or suggest this element, and as such, the presently claimed invention possesses superior properties over the combined teachings of these references. Similarly, it is also now more commonly known that mutations that are causal or predisposing of cancer can be present in normal tissue (*see, e.g., Yap, T. A., Ashok, A., Stoll, J., Mauer, E., Nepomuceno, V. M., Blackwell, K. L., Garber, J. E., & Meric-Bernstam, F. (2022). Prevalence of Germline Findings Among Tumors From Cancer Types Lacking Hereditary Testing Guidelines. JAMA Network Open, 5(5), Article e2213070.*). As opposed to the methods of the claims when read as a whole, the methods described in the Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green references fail to disclose or suggest the omission of mutations that are causal or predisposing of cancer when found in normal tissue as these methods are agnostic to the genetic makeup of a subject.

Claims 11-19, 26, and 28 depend from and include all of the elements of claim 10, and recite additional elements to describe embodiments of particular advantage and utility. Claims 21-25 and 27 depend from and include all of the elements of claim 20, and recite additional elements to describe embodiments of particular advantage and utility. As such, the asserted combination of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green also fails to render the dependent claims obvious.

In view of the foregoing, Applicant submits that claims 10-28, as amended herewith, are in compliance with 35 U.S.C. § 103. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

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G. Rejection under 35 U.S.C. § 101

The Office maintains its rejection of claims 10-25 and rejects newly added claims 26-28 under 35 U.S.C. §101, because the claimed invention is allegedly directed to a judicial exception without significantly more. Applicant respectfully disagrees.

Applicant maintains the positions set forth in the response to the Final Office Action dated April 11, 2022, that the claims should be found to be subject matter eligible under Step 2A prong one (the claims are not directed to the judicial category of a mental process as the claims cannot be practically performed in one's mind), Step 2A prong two (similar to *McRO*, the methods of the present claims present improvements in the technical field of cancer diagnostics), and Step 2B (the methods of the present claims recite additional elements that amount to significantly more than any alleged judicial exception, as they recite elements that are not well-understood, routine, or conventional).

In addition to the positions asserted in response to the Final Office Action dated April 11, 2022, Applicant submits that the claims should further be found to be subject matter eligible at Step 2A prong two of the 101 analysis (as the claims present improvements in the technical field of cancer diagnostics) and Step 2B of the 101 analysis (as the claims recite still further elements that are not well-understood, routine, or conventional).

As described in further detail in response to the 103 rejection, Applicant submits that it is not well-understood, routine, or conventional to generate a first and second set of sequence reads using whole genome sequencing, identify mosaic variants specific to the tissue sample/subject in the first set of sequence reads that is not present in the second set of sequence reads, to identify the mosaic variants specific to the tissue sample/subject in a first additional sample/a second sample, and to provide a report based on the identification of the mosaic variants specific to the tissue sample/subject in the first additional sample/second sample, as recited in claims 10 and 20. Methods contemporaneous to the priority date of the application, such as, for example, those described in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green, were predominantly focused on assaying samples of subjects using predefined panels of known mutations (generally, known cancer driver genes). As these methods were focused on the detection of known mutations using panels that were agnostic to a specific individual, such

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methods would not have contemplated performing whole genome sequencing to detect mosaic variants specific to a tissue sample/subject, assaying a subsequent sample (e.g., a first additional sample, or a second sample (claims 10 and 20, respectively)) to detect a bespoke configuration of mosaic variants specific to the tissue sample/subject, and outputting a report based on the identification of such mosaic variants.

Further, as the elements of the claims that are not well-understood, routine, or conventional result in an assay that is technologically superior to contemporaneous methods (i.e., the methods of the claimed invention result in an assay with improved sensitivity to detect mosaic variants), the methods of the present claims set forth an improvement in the technical field of cancer diagnostics.

In view of the foregoing, Applicant submits that claims 10-30, as amended herewith, are in compliance with 35 U.S.C. § 101. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 101 be withdrawn.

H. Conclusion

For at least the reasons set forth above, it is submitted that claims 10-30 are in condition for allowance. A Notice of Allowance is earnestly solicited.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

The Applicant reserves the right to pursue at a later date any previously pending or other claims that capture any subject matter supported by the present disclosure. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicant has disclaimed or disavowal any subject matter supported by the present application.

Except for issues fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees including fees due under 37 CFR § 1.16 and 1.17, which may be required, and including any required extension of time fees, or credit any overpayment to Deposit Account 15-0665 (Docket Reference: 48929.4008/US03).

Respectfully submitted,

Orrick, Herrington & Sutcliffe LLP

Dated: 11-11-2022

By: /Alex Straughn/
Alex Straughn, Reg. No. 80,155, for
Gargi Talukder, Reg. No. 61,368

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Telephone: (949) 567-6700
Facsimile: (949) 567-6710

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: **John West**	Examiner: **Joseph T Woitach**
U.S. Serial No.: **17/494,513**	Art Unit: **1672**
Filing Date: **October 5, 2021**	Confirmation No.: **8186**
For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Attorney Docket: **48929.4008/US03** Patent No. **11,584,968** Issued: **February 21, 2023**

Via Patent Center
Commissioner for Patents
Office of Data Management
Attention: Certificates of Correction Branch
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT FOR PTO MISTAKE (37 CFR 1.322(a))

Dear Sir:

Attached is Form PTO/SB/44 – Certificate of Correction.

1. On page 40 of the Letters Patent of the above-referenced patent, applicant respectfully requests the following corrections:

Claim 11, Column 55, Lines 37-38, change "multiple nucleotide polymorphisms (HNPs)" to -- multiple nucleotide polymorphisms (MNPs) --.

Claim 16, Column 56, Lines 38-39, delete "from a source or".

Claim 20. Column 56, Lines 57-58, change "multiple nucleotide polymorphisms (HNPs)" to -- multiple nucleotide polymorphisms (MNPs) --.

2. The above-referenced corrections relate to mistakes in the granted patent incurred through the fault of the Office. Please see the amended claims submitted to the Office in the Response to Non-Final Office Action filed November 11, 2022 (copy attached). The claims submitted in the November 11, 2022 were allowed December 15, 2022.

3. Fee and Method of Fee Payment for Certificate of Correction:

☒ To our knowledge, no fees are required.

☐ Attached is a check for _____.

☐ Charge Account 15-0665 ($_____).

☒ If any additional fees are due, please charge Account 15-0665.

4. Please forward the Certificate to the undersigned.

Respectfully submitted,

ORRICK, HERRINGTON & SUTCLIFFE LLI

Dated: March 27, 2023

/Alex Straughn/

Alex Straughn, Reg. No. 80,155
for Gargi Talukder, Reg. No. 61,368

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Tel: 949-567-6700
Fax: 949-567-6710
Customer Number: 34313

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **PERSONALIS, INC.** Serial No.: 17/494,513 Filed: October 5, 2021 For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Group Art Unit: 1672 Examiner: Joseph T. Woitach Customer No. 182685 Confirmation No. 8186 Attorney Docket No. 48929.4008/US03

Filed via Patent Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

Commissioner:

This communication is responsive to the Non-final Office Action of August 29, 2022. This response is being filed on or by November 29, 2022, making it a timely filed response.

Amendments to the Claims begin on page 2 of this paper; and

Remarks begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listing of claims in the application.

1-9. (Canceled)

10. (Currently amended) A method of analyzing a biological sample obtained from a subject being screened for a cancer, wherein the biological sample is from a non-fetal source, the method comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, and wherein (i) said first set of nucleic acid molecules is extracted from tissue sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a blood sample;

(b) using said first set of sequence reads and said second set of sequence reads to identify ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(c) subsequent to (b), identifying said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in a first additional sample of said subject, wherein said first additional sample is obtained from a source that is different than said tissue sample and at a time point that is different than said tissue sample; and

(d) providing a report based on an identification of said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said subject.

11. (Currently amended) The method of claim 10, further comprising identifying ~~one or more second~~ mosaic variants specific to said tissue sample of said subject in a second additional sample of said subject, wherein said second additional sample comprises cell-free DNA, which second additional sample is obtained ~~from a source or~~ at a time point that is different than said tissue sample and said first additional sample.

12. (Currently amended) The method of claim 10, further comprising providing a recommendation for a therapeutic intervention based on an identification of said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject.

13. (Previously presented) The method of claim 10, wherein said tissue sample comprises a metastatic tissue sample, a mixed tissue sample, a biopsy, or a core needle biopsy.

14. (Previously presented) The method of claim 11, wherein said first and/or second additional sample comprises a blood sample, a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.

15. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

16. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are causal or predisposing for a cancer.

17. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are non-causal for a cancer.

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18. (Currently amended) The method of claim ~~11~~ 10, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, or first additional sample~~, or second additional sample~~.

19. (Previously presented) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, first additional sample, or second additional sample.

20. (Currently amended) A method for early disease detection in a subject using at least two samples from the subject, wherein the at least two samples are from a non-fetal source, said method comprising:

(a) obtaining a blood sample from said subject;

(b) extracting (i) a first set of nucleic acid molecules from a first component separated from a blood sample of said subject and (ii) a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample;

(c) quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules present in said first component separated from a blood sample;

(d) comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity;

(e) if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads generated by sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules;

(f) using said first set of sequence reads and said second set of sequence reads to identify ~~one or more first~~ mosaic variants specific to said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(g) subsequent to (f), identifying said ~~one or more first~~ mosaic variants specific to said subject in a second sample of said subject, which second sample is obtained ~~from a source or~~ at a time point that is different than said blood sample; and

(h) providing a report based on an identification of said ~~one or more first~~ mosaic variants specific to said subject in said second sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in said subject.

21. (Previously presented) The method of claim 20, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

22. (Currently amended) The method of claim 20, further comprising identifying ~~one or more second~~ mosaic variants specific to said subject in a third sample of said subject, which third sample is obtained ~~from a source or~~ at a time point that is different than said blood sample and said second sample.

23. (Currently amended) The method of claim 22, wherein said second or third sample comprises a blood sample, ~~a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy,~~ a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.

24. (Currently amended) The method of claim 20, further comprising providing a recommendation for a therapeutic intervention based on an identification of said ~~one or more first~~ mosaic variants specific to said subject.

25. (Currently amended) The method of claim 22 wherein said ~~one or more first and/or second~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

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26. (Currently amended) The method of claim 10, wherein said ~~one or more first~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

27. (Currently amended) The method of claim 20, wherein said ~~one or more first~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

28. (Previously presented) The method of claim 10, wherein said predicting, diagnosing, and/or prognosing of (d) comprises one or more of the following: (i) diagnosing a cancer, (ii) identifying a cancer, (iii) determining a stage of a cancer, (iv) assessing risk of a cancer, (v) assessing risk of cancer recurrence, (vi) assessing reproductive risk, (vii) assessing efficacy of a drug, (viii) assessing risk of an adverse drug reaction, (ix) predicting optimal drug dosage, (x) predicting drug resistance, or any combination thereof.

29. (New) The method of claim 10, wherein said mosaic variants specific to said tissue sample of said subject are identified using capture probes in said first additional sample of step (c).

30. (New) The method of claim 20, wherein said mosaic variants specific to said subject are identified using capture probes in said second sample of step (g).

REMARKS

A. Status of the claims

Claims 10-28 are currently pending in the application. With this amendment, claims 10-12, 15-18, 20, and 22-27 have been amended, and new claims 29 and 30 are added. These amendments are fully supported throughout the specification, including at, for example, paragraphs [0041], [0070], [0076], [0117], [0130], and [0170-0172]. Applicant respectfully requests entry of the claims as amended.

B. Applicant-Initiated Interview Summaries

Applicant would like to thank Examiner Woitach for the opportunity to have a first interview on September 29, 2022, as well as a second interview on November 2, 2022, to discuss the pending application. In accordance with MPEP § 713.04, Applicant provides below summaries of the substance of the interviews.

1. Interview on September 29, 2022

During the first interview, the pending rejections and potential amendments to the claims to overcome the pending rejections were discussed. In addition, with respect to the 35 U.S.C. 101 rejection, possible elements that would be considered under Step 2B as being unconventional were discussed, as were how the combination of steps provides for an integration and significantly more. The Examiner noted that the proposed amendments to the claims were likely to overcome the 112 rejections and the Examiner kindly agreed to review further potential amendments prior to Applicant filing the next response.

2. Interview on November 2, 2022

During the second interview, further potential amendments to the claims were discussed. The Examiner noted that the proposed amendments to the claims had the potential to overcome the remaining rejections pending additional review and searching.

Applicant would like to again thank the Examiner for his time, as well as for consideration of the proposed amendments and supporting arguments thereof.

C. Double Patenting

Claims 10-28 are rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of co-pending Application No. 17/828,572 filed 5/31/2022 (restriction mailed 7/25/2022).

For the purposes of expediting prosecution of the present application, Applicant files herewith a Terminal Disclaimer and respectfully submits that the Office's non-statutory double patenting rejection of claims 10-28 are moot and should be withdrawn.

D. Rejection under 35 U.S.C. § 112(a)

The Office has rejected claims 10-28 under 35 U.S.C. §112(a) as allegedly failing to comply with the written description requirement. Applicant respectfully disagrees.

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended claims 10 and 11 to clarify certain elements of the claims, as suggested by the Office (see, e.g., page 7 of the most recent Office Action). Applicant submits that, in view of the amendments to claims 10 and 11, a person of ordinary skill in the art would readily understand and appreciate the elements of the claims upon review of the specification as a whole.

In view of the foregoing, Applicant respectfully submits that claims 10-28 are in compliance with 35 U.S.C. §112(a). As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112(a) be withdrawn.

E. Rejection under 35 U.S.C. § 112(b)

The Office has rejected claims 10-28 under 35 U.S.C. §112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor regards as the invention. Applicant respectfully disagrees.

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended claims 10 and 11 to clarify certain elements of the claims, as suggested by the Office (see, e.g., page 8 of the most recent Office Action). Applicant

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submits that, in view of the amendments to claims 10 and 11, the claims are not indefinite as there is no longer ambiguity as to what "different" is in reference to when the claims are read in their entirety.

In view of the foregoing, Applicant respectfully submits that claims 10-28 are in compliance with 35 U.S.C. §112(b). As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112(b) be withdrawn.

F. Rejection under 35 U.S.C. § 103

The Office maintains its rejection of claims 10-25 and rejects newly added claims 26-28 under 35 U.S.C. 103 as allegedly being unpatentable over Lo et al. (1997) ("Lo"), Benesova et al. (2013) ("Benesova"), De Mattos-Arruda et al. (2013) ("De Mattos-Arruda"), Laktionov et al. (2004) ("Laktionov"), Ellinger et al. (Urologic Oncology 29:124-129 (2011)) ("Ellinger"), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)) ("Jung"), Shaw et al. (Genome Research 22:220-231 (2012)) ("Shaw"), Lewis et al. (US 2012/0058480 Al) ("Lewis"), and Green et al. (US 2005/0260645 Al) ("Green").

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended independent claims 10 and 20 to clarify certain differences over the asserted combination of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green. Applicant submits that the claims as amended are not obvious in view of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green, because none of the references, alone or in combination, teaches or discloses all of the elements of independent claims 10 and 20.

For example, nothing in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green teaches or discloses, or even suggests, "A method of analyzing a biological sample obtained from a subject being screened for a cancer…wherein **[the] first set of sequence reads and [the] second set of sequences reads are generated using whole genome sequencing**, …**using [the] first set of sequence reads and [the] second set of sequence reads to identify mosaic variants specific to [the] tissue sample in [the] first set of sequence reads that is not present in [the] second set of sequence reads**…**identifying [the] mosaic variants specific to [the] tissue sample of [the] subject in a first additional sample of [the] subject**…

and…**providing a report based on an identification of [the] mosaic variants specific to [the] tissue sample of [the] subject in [the] first additional sample**…," as recited in claim 10 (emphasis added).

Further, nothing in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green teaches or discloses, or even suggests, "A method for early disease detection in a subject using at least two samples from the subject…wherein **[the] first set of sequence reads and [the] second set of sequence reads are generated using whole genome sequencing**…**using [the] first set of sequence reads and [the] second set of sequence reads to identify mosaic variants specific to [the] subject in [the] first set of sequence reads that is not present in [the] second set of sequence reads**…**identifying [the] mosaic variants specific to [the] subject in a second sample of [the] subject**…and…**providing a report based on an identification of [the] mosaic variants specific to [the] subject in [the] second sample**…," as recited in claim 20 (emphasis added).

In addition to the above references not disclosing all elements of the claims, the claimed invention has unexpectedly superior properties when compared to Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green. For example, the methods of the claimed invention perform a comparative analysis of the first set of sequence reads and the second set of sequence reads to identify mosaic variants that are specific to the tissue sample (claim 10) or the individual (claim 20), whereas the references cited in the Office Action merely assay a sample using a predefined panel of mutations that are agnostic to the subject being screened. As such, the claimed methods exhibit technical superiority over the cited references at least for the reason that the claimed methods have a higher sensitivity for the detection of mosaic variants (see, e.g., paragraph [0066] of the specification, as well as the exhibits that were submitted as part of the email correspondence with the Office on October 24, 2022, in conjunction with the interviews with the Examiner), facilitating an earlier detection of disease, such as, for example, cancer. The references cited in the Office Action do not contemplate performing such a comparative analysis due to the simple fact that those references are only concerned with detecting common mutations that are broadly applicable to the human population at large, resulting in a concomitant decrease in assay sensitivity.

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Further, as opposed to the methods discussed in the cited references, the claimed methods are not restricted to the identification of cancer driver genes. As discussed in claims 16 and 17, the methods of the claims allow for the detection of mosaic variants that are causal or predisposing of cancer, as well as mosaic variants that are not causal for cancer. While it is now more commonly known that mosaic variants are present in normal tissue (*see, e.g., Muyas, F., Zapata, L., Guigó, R., & Ossowski, S. (2020). The rate and spectrum of mosaic mutations during embryogenesis revealed by RNA sequencing of 49 tissues. Genome Medicine, 12(1).*), Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green failed to disclose or suggest this element, and as such, the presently claimed invention possesses superior properties over the combined teachings of these references. Similarly, it is also now more commonly known that mutations that are causal or predisposing of cancer can be present in normal tissue (*see, e.g., Yap, T. A., Ashok, A., Stoll, J., Mauer, E., Nepomuceno, V. M., Blackwell, K. L., Garber, J. E., & Meric-Bernstam, F. (2022). Prevalence of Germline Findings Among Tumors From Cancer Types Lacking Hereditary Testing Guidelines. JAMA Network Open, 5(5), Article e2213070.*). As opposed to the methods of the claims when read as a whole, the methods described in the Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green references fail to disclose or suggest the omission of mutations that are causal or predisposing of cancer when found in normal tissue as these methods are agnostic to the genetic makeup of a subject.

Claims 11-19, 26, and 28 depend from and include all of the elements of claim 10, and recite additional elements to describe embodiments of particular advantage and utility. Claims 21-25 and 27 depend from and include all of the elements of claim 20, and recite additional elements to describe embodiments of particular advantage and utility. As such, the asserted combination of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green also fails to render the dependent claims obvious.

In view of the foregoing, Applicant submits that claims 10-28, as amended herewith, are in compliance with 35 U.S.C. § 103. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

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G. Rejection under 35 U.S.C. § 101

The Office maintains its rejection of claims 10-25 and rejects newly added claims 26-28 under 35 U.S.C. §101, because the claimed invention is allegedly directed to a judicial exception without significantly more. Applicant respectfully disagrees.

Applicant maintains the positions set forth in the response to the Final Office Action dated April 11, 2022, that the claims should be found to be subject matter eligible under Step 2A prong one (the claims are not directed to the judicial category of a mental process as the claims cannot be practically performed in one's mind), Step 2A prong two (similar to *McRO*, the methods of the present claims present improvements in the technical field of cancer diagnostics), and Step 2B (the methods of the present claims recite additional elements that amount to significantly more than any alleged judicial exception, as they recite elements that are not well-understood, routine, or conventional).

In addition to the positions asserted in response to the Final Office Action dated April 11, 2022, Applicant submits that the claims should further be found to be subject matter eligible at Step 2A prong two of the 101 analysis (as the claims present improvements in the technical field of cancer diagnostics) and Step 2B of the 101 analysis (as the claims recite still further elements that are not well-understood, routine, or conventional).

As described in further detail in response to the 103 rejection, Applicant submits that it is not well-understood, routine, or conventional to generate a first and second set of sequence reads using whole genome sequencing, identify mosaic variants specific to the tissue sample/subject in the first set of sequence reads that is not present in the second set of sequence reads, to identify the mosaic variants specific to the tissue sample/subject in a first additional sample/a second sample, and to provide a report based on the identification of the mosaic variants specific to the tissue sample/subject in the first additional sample/second sample, as recited in claims 10 and 20. Methods contemporaneous to the priority date of the application, such as, for example, those described in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green, were predominantly focused on assaying samples of subjects using predefined panels of known mutations (generally, known cancer driver genes). As these methods were focused on the detection of known mutations using panels that were agnostic to a specific individual, such

methods would not have contemplated performing whole genome sequencing to detect mosaic variants specific to a tissue sample/subject, assaying a subsequent sample (e.g., a first additional sample, or a second sample (claims 10 and 20, respectively)) to detect a bespoke configuration of mosaic variants specific to the tissue sample/subject, and outputting a report based on the identification of such mosaic variants.

Further, as the elements of the claims that are not well-understood, routine, or conventional result in an assay that is technologically superior to contemporaneous methods (i.e., the methods of the claimed invention result in an assay with improved sensitivity to detect mosaic variants), the methods of the present claims set forth an improvement in the technical field of cancer diagnostics.

In view of the foregoing, Applicant submits that claims 10-30, as amended herewith, are in compliance with 35 U.S.C. § 101. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 101 be withdrawn.

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Foresight v Personalis
IPR2024-00170

H. Conclusion

For at least the reasons set forth above, it is submitted that claims 10-30 are in condition for allowance. A Notice of Allowance is earnestly solicited.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

The Applicant reserves the right to pursue at a later date any previously pending or other claims that capture any subject matter supported by the present disclosure. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicant has disclaimed or disavowal any subject matter supported by the present application.

Except for issues fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees including fees due under 37 CFR § 1.16 and 1.17, which may be required, and including any required extension of time fees, or credit any overpayment to Deposit Account 15-0665 (Docket Reference: 48929.4008/US03).

Respectfully submitted,

Orrick, Herrington & Sutcliffe LLP

Dated: 11-11-2022

By: /Alex Straughn/
Alex Straughn, Reg. No. 80,155, for
Gargi Talukder, Reg. No. 61,368

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Telephone: (949) 567-6700
Facsimile: (949) 567-6710

PTO/SB/44 (09-07)
Approved for use through 03/31/2023. OMB 0651-0033
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(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 11,584,968

APPLICATION NO.: 17/494,513

ISSUE DATE : 02-21-2023

INVENTOR(S) : John West

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 11, Column 55, Lines 37-38, change “multiple nucleotide polymorphisms (HNPs)” to -- multiple nucleotide polymorphisms (MNPs) --.

Claim 16, Column 56, Lines 38-39, delete "from a source or".

Claim 20, Column 56, Lines 57-58, change “multiple nucleotide polymorphisms (HNPs)” to -- multiple nucleotide polymorphisms (MNPs) --.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):

ORRICK, HERRINGTON & SUTCLIFFE LLP
2050 Main Street, Suite 1100
IRVINE, CA 92614

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. 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 1.0 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: Attention Certificate of Corrections Branch, 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 NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	02/21/2023	11584968	48929.4008/US03	8186

182685 7590 02/01/2023

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PAIR WEB site http://pair.uspto.gov for additional inventors):

John West, Cupertino, CA;

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Personalis, Inc., Menlo Park, CA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/494,513	**01/12/2023 12:31:29 PM ET**	**48929.4008/US03**

Title of Invention

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8186	FILED BY	Sheila Gloss
PATENT CENTER #	61426109	FILING DATE	10/05/2021
CUSTOMER #	182685	FIRST NAMED INVENTOR	John West
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Alex Straughn

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
48929_4008US03_IssueFee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	178 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
48929_4008US03_IssueFeeTransmittal.pdf	98EA8789E0A79456E993BB094D35713E23DD6E6280D1754F521BB53717DAC4986E2878BFD42F12D1E96B6CF341BEE3D68E1A3C00651135814F50620FBDAA27DE

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized

by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/494,513	01/12/2023 12:31:29 PM ET	48929.4008/US03

Title of Invention

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

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APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8186	FILED BY	Sheila Gloss
PATENT CENTER #	61426109	AUTHORIZED BY	Alex Straughn
CUSTOMER #	182685	FILING DATE	10/05/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	John West

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 150665	E20231BC34202570	Sheila Gloss

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	600.00	1	600.00
			TOTAL AMOUNT:	$600.00

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

New Applications Under 35 U.S.C. 111

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

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

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage

submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
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By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

182685 7590 12/15/2022

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Sheila Gloss	(Typed or printed name)
/Sheila Gloss/	(Signature)
January 12, 2023	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

TITLE OF INVENTION: METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	03/15/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
WOITACH, JOSEPH T	1672	514-049000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Orrick, Herrington & Sutcliffe, LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Personalis, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Menlo Park, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☒ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 15-0665

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Alex Straughn/ Date January 12, 2023

Typed or printed name Alex Straughn Registration No. 80,155

Foresight EX1108-p. 45
Foresight v Personalis
IPR2024-00170

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 01/09/2023

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1672	

NOTIFICATION DATE	DELIVERY MODE
01/09/2023	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
jmichel@orrick.com
vsantos@orrick.com

Notice of Allowability	Application No. 17/494,513	Applicant(s) West, John	
	Examiner Joseph T Woitach	Art Unit 1672	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 12/21/2022.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 10-30 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☑ Other pto90.

/Joseph Woitach/
Primary Examiner, Art Unit 1672

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
17/494,513	10/05/2021	West, John	48929.4008/US03

	EXAMINER	
ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis) IP Prosecution 2050 Main Street, Suite 1100 IRVINE, CA 92614	Joseph T Woitach	
	ART UNIT	PAPER
	1672	20230104ids

DATE MAILED: _____

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

Commissioner for Patents

The IDS filed 12/16/2022 has been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph T Woitach whose telephone number is (571)272-0739. The examiner can normally be reached on Mon-Fri; 9:00-5:00. 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/interview practice.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R Skowronek can be reached on 571 272-9047. 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.

/Joseph Woitach/
Primary Examiner, Art Unit 1672

PTO-90C (Rev.04-03)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	1	of	2	Attorney Docket Number	48929.4008/US03

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent Document Number	U.S. Patent Document Kind Code[1]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear
	1	US 20130311448 A1		THOMPSON, Douglas	11-21-2013	
	2	US 20160041987 A1		LAPIR, Gennady et al.	02-11-2016	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Office[2]	Foreign Patent Document Number[3]	Foreign Patent Document Kind Code[4]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear	T[6]
	3	WO	2011057061	A1	Quake, Stephen et al.	05-12-2011		

OFFICE ACTIONS/SEARCH REPORTS

Examiner Initials'	Cite No.	Country	Description (*for example*, Office Action (Examiner: J. Doe))	Date of Issuance MM-DD-YYYY	T[6]

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials'	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	4	ANDERSON et al., "Next Generation DNA Sequencing and the Future of Genomic Medicine", Genes 2010, 38-69; doi:10.3390/genes1010038	
	5	CHAN et al., "Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing", Clinical Chemistry 59:1, 211-224 (2013).	
	6	FORSHEW et al., "Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA", Science Translational Medicine, 30 May 2012, Vol. 4, Issue 136, 136ra68; DOI: 10.1126/scitranslmed.3003726.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicants unique citation designation number (optional). [2]See Kinds of U.S. Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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 govern by 35 USC 122 and 37 CFR 1.14. This collection is estimated to take 2 hours 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 are required 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, Mail Stop Amendment, P.O. Box 1450, Alexandria, VA 22313-1450

4164-6362-0419

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /JW/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	2	of	2	Attorney Docket Number	48929.4008/US03

	7	FORSHEW et al., "Noninvasive Identification and Monitoring of Cancer Mutations by Targeted Deep Sequencing of Plasma DNA", SUPPLEMENTARY MATERIALS, Science Translational Medicine, 30 May 2012, Vol. 4, Issue 136, 136ra68; DOI: 10.1126/scitranslmed.3003726.	
	8	GUO et al., "Whole-genome and whole-exome sequencing of bladder cancer identifies frequent alterations in genes involved in sister chromatid cohesion and segregation", nature Genetics, Letters, Vol. 45, No. 12, December 2013. Published online 13 October 2013.	
	9	LEARY et al., "Development of Personalized Tumor Biomarkers Using Massively Parallel Sequencing", Science Translational Medicine, 2010 February 24; 2(20): 20ra14.	
	10	LEY et al., "DNA Sequencing of a cytogenetically normal acute myeloid leukemia genome", Nature, Vol. 456|6 November 2008.	
	11	LIAO et al., "Targeted Massively Parallel Sequencing of Maternal Plasma DNA Permits Efficient and Unbiased Detection of Fetal Alleles", Clinical Chemistry 57:1, 92-101 (2011).	
	12	MAMANOVA et al., "Target-enrichment strategies for next-generation sequencing", Nature Methods, Vol. 7, No. 2, February 2010.	
	13	MERTES et al., "Targeted enrichment of genomic DNA regions for next-generation sequencing", Briefings in Functional Genomics, Vol. 10, No. 6, 374-386, 26 November 2011.	
	14	PODLAHA, Ondrej et al., "Evolution of the cancer genome", Trends Genet. 2012 April ; 28(4): 155-163. doi:10.1016/j.tig.2012.01.003.	
	15	SWANTON, Charles, "Plasma-derived Tumor DNA Analysis at Whole-Genome Resolution," Editorials, Clinical Chemistry 59:1, 6-8; 2013.	
	16	WAGLE, Nikhil et al., "High-Throughput Detection of Actionable Genomic Alterations in Clinical Tumor Samples by Targeted, Massively Parallel Sequencing", Cancer Discovery, January 2012.	
	17	YANG, Yaping et al., "Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders", New England Journal of Medicine, 369;16, October 17, 2013. Published online October 2, 2013.	

Examiner Signature	/Joseph Woitach/	Date Considered	01/04/2023

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				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	1	of	2	Attorney Docket Number	48929.4008/US03

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent Document Number	U.S. Patent Document Kind Code[1]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear
	1	US 20130311448 A1		THOMPSON, Douglas	11-21-2013	
	2	US 20160041987 A1		LAPIR, Gennady et al.	02-11-2016	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Office[2]	Foreign Patent Document Number[3]	Foreign Patent Document Kind Code[4]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear	T[6]
	3	WO	2011057061	A1	Quake, Stephen et al.	05-12-2011		

OFFICE ACTIONS/SEARCH REPORTS

Examiner Initials'	Cite No.	Country	Description (*for example*, Office Action (Examiner: J. Doe))	Date of Issuance MM-DD-YYYY	T[6]

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials'	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/494,513	**12/16/2022 02:42:53 PM ET**	**48929.4008/US03**

Title of Invention

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8186	FILED BY	Sheila Gloss
PATENT CENTER #	61312117	FILING DATE	10/05/2021
CUSTOMER #	182685	FIRST NAMED INVENTOR	John West
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Alex Straughn

Documents

TOTAL DOCUMENTS: 17

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
48929_4008US03_IDSTransmittal_12162022.pdf	4	Transmittal Letter	159 KB
48929_4008US03_IDSForm_12162022.pdf	2	Information Disclosure Statement (IDS) Form (SB08)	207 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
WO2011057061A1_FOR.pdf	42	Foreign Reference	2462 KB
ANDERSON_2010_NPL.pdf	32	Non Patent Literature	516 KB
CHAN_2013_NPL.pdf	14	Non Patent Literature	491 KB

FORSHEW_2012_NPL.pdf	13	Non Patent Literature	921 KB
FORSHEW_SUPPMAT_2012_NPL.pdf	20	Non Patent Literature	1202 KB
GUO_2013_NPL.pdf	7	Non Patent Literature	1159 KB
LEARY_2010_NPL.pdf	16	Non Patent Literature	667 KB
LEY_2008_NPL.pdf	7	Non Patent Literature	213 KB
LIAO_2011_NPL.pdf	10	Non Patent Literature	1272 KB
MAMANOVA_2010_NPL.pdf	9	Non Patent Literature	1157 KB
MERTES_2011_NPL.pdf	13	Non Patent Literature	324 KB
PODLAHA_2012_NPL.pdf	16	Non Patent Literature	1638 KB
SWANTON_2013_NPL.pdf	3	Non Patent Literature	70 KB
WAGLE_2012_NPL.pdf	12	Non Patent Literature	1359 KB
YANG_2013_NPL.pdf	10	Non Patent Literature	1253 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
48929_4008US03_IDSTransmittal_12162022.pdf	6A2C17F074D5506D2286B81D78C994F5FCAF09AF5693675150E13B4B44826225C5B971780B0C1CDBBA0BF322C66665BD41AD02DA1D0FAA43E96DBE7ACD5CA8A9
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New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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NOTICE OF ALLOWANCE AND FEE(S) DUE

182685 7590 12/15/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER
WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 12/15/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

TITLE OF INVENTION: METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	03/15/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

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I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

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182685 7590 12/15/2022

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

TITLE OF INVENTION: METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$600	$0.00	$0.00	$600	03/15/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
WOITACH, JOSEPH T	1672	514-049000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

Foresight EX1108-p. 58
Foresight v Personalis
IPR2024-00170

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 12/15/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	**PAPER NUMBER**
1672	

DATE MAILED: 12/15/2022

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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Foresight v Personalis
IPR2024-00170

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. 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.

Notice of Allowability	Application No. 17/494,513	Applicant(s) West, John	
	Examiner Joseph T Woitach	Art Unit 1672	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 11/11/2022.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 10-30 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Joseph Woitach/
Primary Examiner, Art Unit 1672

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

RCE TrackOne Request

Applicants request filed 8/4/2022 was been granted (see paper mailed 8/12/2022).

Applicants response filed 11/14/2022 to the non-final office action mailed 8/29/2022 did not require an extension of time.

Applicant's Amendment

Applicant's amendment filed 11/11/2022 has been received and entered. Claims 10-12, 15-18, 20, 22-27 have been amended, claims 1-9 have been cancelled and claims 29-30 have been added.

Claims 10-30 are pending.

Election/Restriction

Applicant's election without traverse of Group II, and the species of a blood sample and SNPs in the reply filed on 2/9/2022 was acknowledged. Upon search and review of the specification it did not appear to be a burden to examine both groups, and the restriction requirement **was withdrawn.**

Newly added claims 29-30 are dependent on the pending claims and appear consistent with the elected invention.

Claims 10-30 are pending and currently under examination as drawn to a method of analyzing a biological sample by comparing sequence reads obtained from a blood component and the comparison to samples taken at a different time from the first for patient screening are currently under examination.

Priority

This application filed 10/5/2021 is a Divisional of 16/132123, now US Patent 11142802, which is a continuation of 14/929075, now US Patent 10125399, which claims benefit to US provisional application 62/072936 filed 10/30/2014; and is related to 17/065406 filed 10/7/2020 through parent 16/132123, and to PCT/US15/58483 filed 10/30/2015; and is the parent to US application 17/748200 filed 5/19/2022, which is the parent US application 17/828572 filed 5/31/2022.

No comment on the priority summary is provided by Applicants in the instant response.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 11/11/2022 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

It is noted that some listed references have been crossed off because they do not contain a publication date. However, they have been reviewed and considered as part of the record.

Double Patenting

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).

Claims 10-28 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of copending Application No. 17/828572 filed 5/31/2022 (FAOM mailed 9/13/2022) **is withdrawn.**

The terminal disclaimer filed 11/11/2022 was received and **APPROVED**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-29 rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement **is withdrawn.**

In view of the claim amendments, it is agreed the claims as a whole are clear and supported by the instant application.

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-28 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention for the limitations of 'additional sample' that is 'different' (see step (c) as amended and claim 11 for example which appears to require another different source be used) **is withdrawn.**

The amendments to the claims have obviated the basis of the rejection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10-28 rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter because the claimed invention is not directed to patent eligible subject matter **is withdrawn.**

Claim analysis

Independent claims 10 and 20 have been amended and still are directed generally towards a method of screening for cancer by detecting variants from a tissue as compared to a reference of leukocytes present in the blood of a patient, and reporting possible observed changes over time. The claims have been amended to require that the sequence reads be obtained through whole genome sequencing and require that the first sample is a tissue, provide for additional specificity to the identification of subsequent samples, and that the final step provides for a report of any identification of a variant and that the variant is correlated to predicting, diagnosing, and/or prognosing a status or outcome of a cancer. The claim sets forth the steps of obtaining reads for two samples from a subject, one representing a tissue and one representing leukocytes, and subsequent steps provide additional samples from a tissue or blood, obtaining reads of the nucleic acids reads that are present in the samples by sequencing the nucleic acids that are present, and comparing the sequence data identifying possible variants that may be present between the two where the reads from the leukocytes is to be designated 'normal' in the analysis. Claim 20 has been amended consistently with claim 10, and still is directed to separating blood into cfDNA and leukocytes to obtain samples which are sequences and the reads produced are used in the analysis over time. Dependent claims set forth the types of variations that might be detected, such as copy number, SNPs, MNPs, inDels,.. or that the variant is associated with disease and/or possible treatment and that the method steps can be performed more than once at different time points for comparison of the variants at different times.

For step 1 of the 101 analysis, claims 10-30 are found to be directed to a statutory category of a process. As amended the claims require obtaining reads by sequencing nucleic acid molecules obtained from the biological samples of the patient for comparison and analysis of differences in the read data between the two samples.

For step 2A of the 101 analysis, the judicial exception of the claims are the steps of accessing and analyzing sequence read data for differences/variants. The step of aligning and comparing sequence to arrive at the identification of variations between sequences are considered instructional steps. In view of the specification, the claim requires analyzing homology or computing similarity scores to determine differences in the two sources of sequence reads. The judicial exception is a set of instructions for analysis of sequence data, and appears to fall into the category of Mental Processes that is concepts performed in the human mind (including an observation, evaluation, judgment, opinion). However, as amended the claims require that the reads generated from whole genome sequencing be generated and used in the comparison of the reads, and that variations between the two termed as mosaic variants are identified which appears to beyond the ability of simply one's mind or a task performed on paper. Additionally, the claims require the use of the observed variants in subsequent analysis steps of additional samples at different time point than the first comparison. Here, while the claims do not explicitly require a system or computer for the analysis steps, given the large amount and complexity of read sequence data from whole genome sequencing and the requirement for the identification of the mosaic variants that exist for subsequent monitoring steps, the claims appear to not be simply directed to judicial exception.

Additionally, recent guidance from the office requires that the judicial exception be evaluated under a second prong to determine whether the judicial exception is practically

applied. In the instant case, the evidence of record provides that in practicing the claims obtaining reads from whole genome sequencing and identifying the mosaic variants better allows one to analyze in subsequent steps subjects suspected to have cancer given the number and ability to use the many variants which would exist between the initial two samples.

Accordingly, for the reasons above and of record, the rejection **is withdrawn.**

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 10-28 rejected under 35 U.S.C. 103 as being unpatentable over Lo et al. (1997), Benesova et al. (2013), De Mattos-Arruda et al. (2013), Laktionov et al. (2004), Ellinger et al (Urologic Oncology 29:124-129 (2001)), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)), Shaw et al (Genome Research 22:220-231 (2012)), Lewis et al. (US 2012/0058480 A1) and Green et al. (US 2005/0260645 A1) **is withdrawn.**

While Benesova et al provide recent development in methodologies allows screening for a presence of cell-free DNA as a new viable tool in early detection and management of major cancers, the methods of Benesova et al provide the step to distinguish tumor cfDNA from nontumorous cfDNA through the analysis of specific somatic DNA mutations present in the primary tumor tissue, not any and all possible mosaic variants present in whole genome read data. Similarly, Lo et al provide a report for the presence of cfDNA in maternal plasma and serum, and the use of a sensitive Y-PCR assay to detect circulating male fetal DNA from women bearing male fetuses but fail to provide the use of whole genome analysis and the general use of mosaic variants as provided by the present claims. Accordingly, the rejection **is withdrawn.**

Conclusion

Claims 10-30 are allowed.

In the art of record, Lo et al. (1997) provide specific method steps for separating and comparing the two nucleic acid sources present in a blood sample however do not provide the teaching or motivation for whole genome sequencing, or the application of the information obtained in subsequent steps of cancer patient monitoring. While some of the individual variants detected may be informative for a particular type of cancer, the use of the identified mosaic

variants in monitoring steps for reporting predicting, diagnosing, and/or prognosing a status or outcome of a cancer in a subject provides a much more sensitive means to detect the presence of cancer in the subject than single alterations.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph T Woitach whose telephone number is (571)272-0739. The examiner can normally be reached Mon-Fri; 9:00-5:00.

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, Karlheinz R Skowronek can be reached on 571 272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Joseph Woitach/
Primary Examiner, Art Unit 1631

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	**Art Unit**
	Joseph T Woitach	1672

CPC								
Symbol							**Type**	**Version**
C12Q	/	1	/	6886			F	2013-01-01
A61K	/	31	/	7068			I	2013-01-01
G16B	/	45	/	00			I	2019-02-01
C12Q	/	2600	/	156			A	2013-01-01
C12Q	/	1	/	6809			A	2013-01-01
C12Q	/	1	/	6827			A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
C12Q	/	1	/	6809	A	1	1	2013-01-01
C12Q	/	2535	/	122	A	1	2	2013-01-01
C12Q	/	1	/	6827	A	2	1	2013-01-01
C12Q	/	2535	/	122	A	2	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	21	
/Joseph Woitach/ Primary Examiner, Art Unit 1672	05 December 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1, 20	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	**Art Unit**
	Joseph T Woitach	1672

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C12Q1/6886	/	1	/	6886
C12Q1/6809	/	1	/	6809
C12Q1/6827	/	1	/	6827

NON-CLAIMED				
A61K31/7068	/	31	/	7068
G16B45/00	/	45	/	00

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE (Assistant Examiner) (Date)	**Total Claims Allowed:** 21	
/Joseph Woitach/ Primary Examiner, Art Unit 1672 (Primary Examiner) 05 December 2022 (Date)	O.G. Print Claim(s) 1, 20	O.G. Print Figure none

U.S. Patent and Trademark Office Part of Paper No.: 20221123

Foresight EX1108-p. 72
Foresight v Personalis
IPR2024-00170

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	**Art Unit**
	Joseph T Woitach	1672

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	10	10	18	19	24										
2	11	11	26	20	27										
3	14	12	28	21	30										
4	15	13	29												
5	16	14	20												
6	17	15	21												
7	19	16	22												
8	12	17	23												
9	13	18	25												

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	21	
/Joseph Woitach/ Primary Examiner, Art Unit 1672	05 December 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1, 20	none

U.S. Patent and Trademark Office

Part of Paper No.: 20221123

Foresight EX1108-p. 73
Foresight v Personalis
IPR2024-00170

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	Art Unit
	Joseph T Woitach	1672

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.

/Joseph Woitach/ Primary Examiner, Art Unit 1672	

Foresight EX1108 p.74
Foresight v Personalis
IPR2024-00170

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	**Art Unit**
	Joseph T Woitach	1672

Search Notes		
Search Notes	**Date**	**Examiner**
reviewed applications/patents in priority listing	02/17/2022	jw
PALM for inventor and assignee/applicant	02/17/2022	jw
Google	02/17/2022	jw
SEARCH	02/17/2022	jw
Google	04/04/2022	jw
SEARCH	04/04/2022	jw
PALM for related applications by inventor and Applicant/assignee	04/04/2022	jw
global portfolio	04/04/2022	jw
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reviewed related applications prosecution	08/15/2022	jw
global dossier	08/15/2022	jw
PALM for inventors and assignee	08/15/2022	jw
SEARCH	12/04/2022	jw
Google	12/04/2022	jw
global dossier	12/04/2022	jw
review ODP '572	12/04/2022	jw

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
text search	no symbol search		jw

/Joseph Woitach/ Primary Examiner, Art Unit 1672	

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Foresight v Personalis
IPR2024-00170

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	1	of	4	Attorney Docket Number	48929.4008/US03

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent Document Number	Kind Code[1]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear
	1	US-20160283484		CHANDRATILLAKE et al.	09-29-2016	
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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicants unique citation designation number (optional). [2]See Kinds of U.S. Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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 govern by 35 USC 122 and 37 CFR 1.14. This collection is estimated to take 2 hours 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 are required 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, Mail Stop Amendment, P.O. Box 1450, Alexandria, VA 22313-1450

4146-0547-5906

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /JW/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	2	of	4	Attorney Docket Number	48929.4008/US03

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Examiner Initials	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear	T[6]
		Office[2]	Number[3]	Kind Code[4]				

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials'	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	51	NG, et al. Targeted capture and massively parallel sequencing of 12 human exomes. Nature. 2009 Sep 10;461(7261):272-6. doi: 10.1038-nature08250. Epub 2009 Aug 16.	

Examiner Signature		Date Considered	

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				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	3	of	4	Attorney Docket Number	48929.4008/US03

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Examiner Signature		Date Considered	

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				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	4	of	4	Attorney Docket Number	48929.4008/US03

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Examiner Signature	/Joseph Woitach/	Date Considered	12/05/2022

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicants unique citation designation number (optional). [2]See Kinds of U.S. Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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4146-0547-5906

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /JW/

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L97	466	woitach	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	OFF	2022/10/31 10:08 AM
L102	21356	evaluable	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	OFF	2022/11/02 05:21 PM
L103	13	evaluable AND (phase NEAR variant)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	OFF	2022/11/02 05:21 PM
L130	2887	CRISPR.clm. AND (cluster OR clustering) AND matrix	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	OFF	2022/12/03 05:52 PM
L131	520652	(mosaic OR allele)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	OFF	2022/12/05 10:58 AM
L132	4223030	(mosaic OR allele OR variant OR mutation) AND ((total OR all OR (genome AND whole) OR WGS))	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	OFF	2022/12/05 11:00 AM
L133	147510	(mosaic OR allele OR variant OR mutation) AND ((total OR all OR (genome AND whole) OR WGS)) AND (cfDNA OR (cell NEAR free))	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	OFF	2022/12/05 11:01 AM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

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Foresight v Personalis
IPR2024-00170

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	1	of	6	Attorney Docket Number	48929.4008/US03

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	1	US-20020006615		GOLDSBOROUGH et al.	01-17-2002	
	2	US-20020164629		QUAKE, Stephen et al.	11-07-2002	
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Examiner Signature	/Joseph Woitach/	Date Considered	12/05/2022

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Bibliographic Data

Application No: 17/494,513

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /Joseph Woitach/ Examiner's Signature | Initials

Title: METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/05/2021	514	1672	48929.4008/US03
RULE			

APPLICANTS

Personalis, Inc., Menlo Park, CA, UNITED STATES

INVENTORS

John West, Cupertino, CA, UNITED STATES

CONTINUING DATA

This application is a DIV of 16132123 09/14/2018 PAT 11142802

16132123 is a CON of 14929075 10/30/2015 PAT 10125399

14929075 has PRO of 62072936 10/30/2014

FOREIGN APPLICATIONS

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Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 17/494,513 *	17/494,513	West, John	
	Examiner	**Art Unit**	
	WOITACH, JOSEPH T	1672	

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Docket Number (Optional): 48929.4008/US03

In re Application of: Personalis, Inc.

Application No.: 17/494,513

Filed: October 5, 2021

For: METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

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				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	1	of	6	Attorney Docket Number	48929.4008/US03

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Examiner Initials	Cite No.	U.S. Patent Document Number	Kind Code[1]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear
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				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	2	of	6	Attorney Docket Number	48929.4008/US03

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	51	EP-0281927-B1			BAYER CORPORATION	06-28-1995		
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				Examiner Name	Joseph T. Woitach
Sheet	3	of	6	Attorney Docket Number	48929.4008/US03

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	60	WO-2011091046-A1	VERINATA HEALTH INC [US], et al.	07-28-2011		
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	62	WO-2011160206-A1	MORIN RYAN D [CA], et al.	12-29-2011		
	63	WO-2012142611-A2	COMPLETE GENOMICS INC [US], et al.	10-18-2012		
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	67	WO-2015051275-A1	PERSONALIS INC [US]	04-09-2015		

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				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	4	of	6	Attorney Docket Number	48929.4008/US03

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/494,513	**11/11/2022 04:24:49 PM ET**	**48929.4008/US03**

Title of Invention

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8186	FILED BY	Sheila Gloss
PATENT CENTER #	61170559	FILING DATE	10/05/2021
CUSTOMER #	182685	FIRST NAMED INVENTOR	John West
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Alex Straughn

Documents

TOTAL DOCUMENTS: 102

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
48929_4008US03_Response_NFOA.pdf		14	-	185 KB
48929_4008US03_Response_NFOA-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	108 KB
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48929_4008US03_Response_NFOA-REM.pdf	(7-14)	8	Applicant Arguments/Remarks Made in an Amendment	175 KB
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Digest

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TURAJLIK_SupplementaryFigures_NPL.pdf	B3BADA0FD4375484547EA547864855ECF37D6CC11FFD5CB041FAD95629DBDE0CF5299263886B69DD29E2CB5BA9DF90B2B63776654805E5CFC479E70670B9BBAF
TEWHEY_2009_NPL.pdf	FFA9BF7C6887342009A730D4AC66D63A768818D2DBB2AD040EBC0E3290DBE524354304C528EBC225F9B3848BB9A1AE0A169F8DF273A42DE47DB96DC10417F8E7
TURAJLIK_SupplementaryTables_NPL.pdf	8F08172E398DD0B1826C54163B30A9387F9F5EBFD57BB9F36BB373455225F6695FB309F2EED6A38B7B5108578F8ACE609AC8B6E0A82292BE6C461A7F7C27E1AF
VANDRIEL_2006_NPL.pdf	8DBB968CEAB3D78911CBA68DAA3D936479AEC0A485816BE759B8B6853F98D2EA9D18A65E98DDB6D3C2F38E04511127A08A1E85110EE176CC24B8D81AB8C97A60

VELCULESCU_1995_NPL.pdf	A02675D237B2303B57D6F5EA110075E02F92E34790E87DE004BB637E29BED49E8208454C37F0C4CFD0CB58D81A393760EB9C69AC7CCCA6E4B724EE0E130F92EC
VarScan_2009_NPL.pdf	66C21A91B93EC7C5A664E9D9ED69D3034204ED37B1DC1C58BE8D93AAEA93BCC9D04C187F7F4A8F65CA57AFEF220B972B02FB7378CFC0AA5225CF9B9E8FF98A59

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	1	of	4	Attorney Docket Number	48929.4008/US03

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent Document Number	Kind Code[1]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear
	1	US-20160283484		CHANDRATILLAKE et al.	09-29-2016	
	2	US-20170253921		LIU, Chunmei et al.	09-07-2017	
	3	US-20190211406 A1		BABIARZ, Joshua et al.	07-11-2019	
	4	US-20210062258 A1		BARTHA, Gabor T. et al.	03-04-2021	
	5	US-20210398609 A1		SIGURJONSSON, Styrmir et al.	12-23-2021	
	6	US-4458066		CARUTHERS, M. H. et al.	07-03-1984	
	7	US-4683202		MULLIS, Kary B.	07-28-1987	
	8	US-5143854		PIRRUNG, Michael C. et al.	09-01-1992	
	9	US-5382510		LEVINE, Arnold J. et al.	01-17-1995	
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	11	US-5432065		FULLER, Carl W.	07-11-1995	
	12	US-5472672		BRENNAN, Thomas M.	12-05-1995	
	13	US-6045996		CRONIN, Maureen T. et al.	04-04-2000	
	14	US-6754655		SEGAL, Michael M.	06-22-2004	
	15	US-6818395		QUAKE et al.	11-16-2004	
	16	US-7169560		LAPIDUS et al.	01-30-2007	
	17	US-7211390		ROTHBERG et al.	05-01-2007	
	18	US-7211654		GAO, Xiaolian et al.	05-01-2007	
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	20	US-7264929		ROTHBERG et al.	09-04-2007	
	21	US-7280922		MEI, Rui et al.	10-09-2007	
	22	US-7282337		HARRIS	10-16-2007	
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	24	US-7323305 B2		LEAMON et al.	01-29-2008	
	25	US-7335762 B2		ROTHBERG et al.	02-26-2008	
	26	US-7361488 B2		FAN, Jian-Bing et al.	04-22-2008	
	27	US-7534561 B2		SANA, Theodore R. et al.	05-19-2009	
	28	US-7582420 B2		OLIPHANT, Arnold et al.	09-01-2009	
	29	US-7785783 B2		MORLEY, Alexander et al.	08-31-2010	
	30	US-8026094 B2		GREEN, Roland et al.	09-27-2011	
	31	US-8140270-B2		KINGSMORE, Stephen F. et al.	03-20-2012	

Examiner Signature		Date Considered	

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4146-0547-5906

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				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	2	of	4	Attorney Docket Number	48929.4008/US03

	32	US-8415101	GARNER, Harold R.	04-09-2013	
	33	US-8417459 B2	REESE, Marin et al.	04-09-2013	
	34	US-8532930 B2	RABINOWITZ, Matthew et al.	09-10-2013	
	35	US-8589175 B2	GLAUSER, Tracy et al.	11-19-2013	
	36	US-8785353 B2	VAN EIJK, Michael et al.	07-22-2014	
	37	US-8862410 B2	HATCHWELL, Eli et al.	10-14-2014	
	38	US-9109256 B2	SHUBER, Anthony	08-18-2015	
	39	US-9183496-B2	HARRIS, Jason et al.	11-10-2015	
	40	US-9228232 B2	FAHAM, Malek et al.	01-05-2016	
	41	US-9416422 B2	CHEUNG, Nai-Kong	08-16-2016	
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	45	US-9727692-B2	HARRIS, Jason et al.	08-08-2017	
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	50	US-10255330	CHANDRATILLAKE et al.	03-20-2019	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document			Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear	T[6]
		Office[2]	Number[3]	Kind Code[4]				

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials'	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	51	NG, et al. Targeted capture and massively parallel sequencing of 12 human exomes. Nature. 2009 Sep 10;461(7261):272-6. doi: 10.1038-nature08250. Epub 2009 Aug 16.	

Examiner Signature		Date Considered	

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Sheet	4	of	4	Attorney Docket Number	48929.4008/US03

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: **John West**	Examiner: **Joseph T. Woitach**
U.S. Serial No.: **17/494,513**	Art Unit: **1672**
Filing Date: **October 5, 2021**	Confirmation No.: **8186**
For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Attorney Docket: **48929.4008/US03**

Via Patent Center
Commissioner for Patents

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Sir:

In accordance with 37 CFR §§ 1.97 and 1.98, the items identified in this Information Disclosure Statement ("IDS") are brought to the attention of the Office. The items are listed on the attached form PTO/SB/08a (PTO-1449). In accordance with the USPTO waiver of the requirement under 37 CFR § 1.98(a)(2)(i), only copies of foreign patent documents and non-patent literature are enclosed for the convenience of the Examiner.

The items identified in this IDS may or may not be "material" pursuant to 37 CFR § 1.56. The submission thereof by Applicant is not to be construed as an admission that any such patent, publication or other information referred to therein is material or considered to be material (37 CFR § 1.97(h)), or even qualifies as "prior art" under 35 USC § 102 with respect to this invention unless specifically designated by Applicant as such.

INFORMATION DISCLOSURE STATEMENT FILING PROVISION:

☐ This IDS is believed to be timely in that it is being submitted under 37 CFR § 1.97(b), that is (1) within three months of the filing date of the application, which is not a continued prosecution application filed under § 1.53(d); or (2) within three months of entry of the national stage as set forth in 37 CFR § 1.491; or (3) before the mailing of a first Office Action on the merits; or (4) before the mailing of a first Office Action after filing a request for continued examination under § 1.114. Thus, no fee is required.

Foresight EX1108-p. 122
Foresight v Personalis
IPR2024-00170

☐ However, if the undersigned is in error in this regard, Applicant respectfully requests that the Office consider this IDS as filed under 37 CFR § 1.97(c), if applicable, and charge the fee due under 37 CFR §1.17(p) to the deposit account referenced below.

☐ However, if the undersigned is in error in this regard, Applicant respectfully requests that the Office consider this IDS as filed under 37 CFR § 1.97(c), if applicable, and a statement under 37 CFR § 1.97(e) is included below, thus no fee is required.

☒ This IDS is being submitted under 37 CFR § 1.97(c), that is after mailing of a first Office Action on the merits, but before a Final Action under 37 CFR § 1.113 or a Notice of Allowance under 37 CFR § 1.311.

☒ The fee due under 37 CFR § 1.17(p) is submitted herewith.

☐ A statement under 37 CFR § 1.97(e) is included below, thus no fee is required. In the event that this IDS is not received before a Final Action or a Notice of Allowance, then Applicant respectfully requests that the Office consider the filing of these papers to be submitted under 37 CFR § 1.97(d) and charge the fee due under 37 CFR § 1.17(p) to the deposit account below.

☐ This IDS is being submitted under 37 CFR § 1.97(d), that is after a Final Action under 37 CFR § 1.113 or a Notice of Allowance under 37 CFR § 1.311, but before payment of the issue fee. A statement under 37 CFR § 1.97(e) is included below. The fee due under 37 CFR § 1.17(p) is submitted herewith ($260.00 – large entity).

☐ This IDS is being submitted after a payment of the issue fee. A statement under 37 CFR § 1.97(e) is included below. The Certification and Request for Reconsideration of an IDS filed after payment of the issue fee under QPDIS Pilot Program is included. The EFS-Web e-petition is included. The fee due under 37 CFR § 1.17(p) is submitted herewith ($260.00 – large entity).

STATEMENT UNDER 37 CFR § 1.97(e):

☐ Each item contained in this IDS 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 this IDS.

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

STATEMENT UNDER 37 CFR § 1.98(d)(1):

☐ Copies of patents, publications, pending US applications or other information, as specified in 37 CFR § 1.98(a), listed on the Information Disclosure Statement are NOT required. The subject application is a continuation, divisional, or continuation-in-part, and relies on the earlier application for an effective filing date under 35 USC § 120.

MCKESSON STATEMENT

☐ In accordance with M.P.E.P. 2001.06(b) and in view of McKesson Information Solutions v. Bridge Medical (Fed. Cir. 2007), Applicant wishes to inform/remind the Examiner that this application is related to the following U.S. Patent Application(s):

U.S. Application No. **, filed **

The Examiner is encouraged to review the art made of record, any Office Action, and any Notice of Allowance in the above-mentioned related application(s). Applicant assumes that due to the ease of review on PAIR by the Examiner, Applicant need not submit copies of the individual Office Actions and/or Notices of Allowance. Applicant assumes that the Examiner is aware that prosecution is ongoing in the identified application(s) and that the Examiner will continue to evaluate the application(s) as needed. The identification of the above related application(s) is not to be construed as a waiver of secrecy as to the application(s) now or upon issuance of the present application as a patent.

STATEMENT UNDER 37 CFR § 1.704(d):

☐ Each item contained in this IDS was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

☐ Each item contained in this IDS was a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

PAYMENT AND/OR AUTHORIZATION TO CHARGE FEES:

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☒ The Commissioner is authorized to charge any fees required by the filing of these papers, and to credit any overpayment to Orrick, Herrington & Sutcliffe's Deposit Account No. **15-0665**.

Respectfully submitted,

Orrick, Herrington & Sutcliffe LLP

Dated: 11-11-2022

By: /Alex Straughn/
Alex Straughn, Reg. No. 80,155, for
Gargi Talukder, Reg. No. 61,368

ORRICK, HERRINGTON & SUTCLIFFE LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
949/567-6700 Telephone 949/567-6710 Facsimile

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1672
				Examiner Name	Joseph T. Woitach
Sheet	1	of	1	Attorney Docket Number	48929.4008/US03

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent Document Number	Kind Code[1]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear
	1	US-10262103 B2		LEHRER, Raphael et al.	04-16-2019	
	2	US-10266890		BARTHA, Gabor T. et al.	04-23-2019	
	3	US-10415091		BARTHA, Gabor T. et al.	09-17-2019	
	4	US-10450611		WEST et al.	10-22-2019	
	5	US-10597717 B2		MAGUIRE et al.	03-24-2020	
	6	US-10711306 B2		SHIINA, Takashi et al.	07-14-2020	
	7	US-10738355 B2		SAHIN, Ugur et al.	08-11-2020	
	8	US-10741269 B2		CHUDOVA, Darya et al.	08-11-2020	
	9	US-10801070 B2		CLEMENT, Mark et al.	10-13-2020	
	10	US-10900088 B2		VOGELSTEIN, Bert et al.	01-26-2021	
	11	US-11047006 B2		SALK, Jesse et al.	06-29-2021	
	12	US-11062789 B2		CHIU, Rossa Wai Kwun et al.	07-13-2021	
	13	US-11142797 B2		Moynahan, Mary et al.	10-12-2021	
	14	US-11155867		BARTHA, Gabor T. et al.	10-26-2021	
	15	US-11286530 B2		RABINOWITZ, Matthew et al.	03-29-2022	

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Office[2]	Number[3]	Kind Code[4]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear	T[6]

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials'	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicants unique citation designation number (optional). [2]See Kinds of U.S. Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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 govern by 35 USC 122 and 37 CFR 1.14. This collection is estimated to take 2 hours 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 are required 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, Mail Stop Amendment, P.O. Box 1450, Alexandria, VA 22313-1450

4157-1283-7698

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **PERSONALIS, INC.** Serial No.: 17/494,513 Filed: October 5, 2021 For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Group Art Unit: 1672 Examiner: Joseph T. Woitach Customer No. 182685 Confirmation No. 8186 Attorney Docket No. 48929.4008/US03

Filed via Patent Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

Commissioner:

This communication is responsive to the Non-final Office Action of August 29, 2022. This response is being filed on or by November 29, 2022, making it a timely filed response.

Amendments to the Claims begin on page 2 of this paper; and

Remarks begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listing of claims in the application.

1-9. (Canceled)

10. (Currently amended) A method of analyzing a biological sample obtained from a subject being screened for a cancer, wherein the biological sample is from a non-fetal source, the method comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, and wherein (i) said first set of nucleic acid molecules is extracted from tissue sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a blood sample;

(b) using said first set of sequence reads and said second set of sequence reads to identify ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(c) subsequent to (b), identifying said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in a first additional sample of said subject, wherein said first additional sample is obtained from a source that is different than said tissue sample and at a time point that is different than said tissue sample; and

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(d) providing a report based on an identification of said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said subject.

11. (Currently amended) The method of claim 10, further comprising identifying ~~one or more second~~ mosaic variants specific to said tissue sample of said subject in a second additional sample of said subject, wherein said second additional sample comprises cell-free DNA, which second additional sample is obtained ~~from a source or~~ at a time point that is different than said tissue sample and said first additional sample.

12. (Currently amended) The method of claim 10, further comprising providing a recommendation for a therapeutic intervention based on an identification of said ~~one or more first~~ mosaic variants specific to said tissue sample of said subject.

13. (Previously presented) The method of claim 10, wherein said tissue sample comprises a metastatic tissue sample, a mixed tissue sample, a biopsy, or a core needle biopsy.

14. (Previously presented) The method of claim 11, wherein said first and/or second additional sample comprises a blood sample, a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.

15. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

16. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are causal or predisposing for a cancer.

17. (Currently amended) The method of claim 11, wherein said ~~one or more first and/or second~~ mosaic variants specific to said tissue sample of said subject are non-causal for a cancer.

18. (Currently amended) The method of claim ~~11~~ 10, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, or first additional sample~~, or second additional sample~~.

19. (Previously presented) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, first additional sample, or second additional sample.

20. (Currently amended) A method for early disease detection in a subject using at least two samples from the subject, wherein the at least two samples are from a non-fetal source, said method comprising:

(a) obtaining a blood sample from said subject;

(b) extracting (i) a first set of nucleic acid molecules from a first component separated from a blood sample of said subject and (ii) a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample;

(c) quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules present in said first component separated from a blood sample;

(d) comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity;

(e) if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads generated by sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules;

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(f) using said first set of sequence reads and said second set of sequence reads to identify ~~one or more first~~ mosaic variants specific to said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(g) subsequent to (f), identifying said ~~one or more first~~ mosaic variants specific to said subject in a second sample of said subject, which second sample is obtained ~~from a source or~~ at a time point that is different than said blood sample; and

(h) providing a report based on an identification of said ~~one or more first~~ mosaic variants specific to said subject in said second sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in said subject.

21. (Previously presented) The method of claim 20, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

22. (Currently amended) The method of claim 20, further comprising identifying ~~one or more second~~ mosaic variants specific to said subject in a third sample of said subject, which third sample is obtained ~~from a source or~~ at a time point that is different than said blood sample and said second sample.

23. (Currently amended) The method of claim 22, wherein said second or third sample comprises a blood sample, ~~a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy,~~ a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.

24. (Currently amended) The method of claim 20, further comprising providing a recommendation for a therapeutic intervention based on an identification of said ~~one or more first~~ mosaic variants specific to said subject.

25. (Currently amended) The method of claim 22 wherein said ~~one or more first and/or second~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

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26. (Currently amended) The method of claim 10, wherein said ~~one or more first~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

27. (Currently amended) The method of claim 20, wherein said ~~one or more first~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

28. (Previously presented) The method of claim 10, wherein said predicting, diagnosing, and/or prognosing of (d) comprises one or more of the following: (i) diagnosing a cancer, (ii) identifying a cancer, (iii) determining a stage of a cancer, (iv) assessing risk of a cancer, (v) assessing risk of cancer recurrence, (vi) assessing reproductive risk, (vii) assessing efficacy of a drug, (viii) assessing risk of an adverse drug reaction, (ix) predicting optimal drug dosage, (x) predicting drug resistance, or any combination thereof.

29. (New) The method of claim 10, wherein said mosaic variants specific to said tissue sample of said subject are identified using capture probes in said first additional sample of step (c).

30. (New) The method of claim 20, wherein said mosaic variants specific to said subject are identified using capture probes in said second sample of step (g).

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REMARKS

A. Status of the claims

Claims 10-28 are currently pending in the application. With this amendment, claims 10-12, 15-18, 20, and 22-27 have been amended, and new claims 29 and 30 are added. These amendments are fully supported throughout the specification, including at, for example, paragraphs [0041], [0070], [0076], [0117], [0130], and [0170-0172]. Applicant respectfully requests entry of the claims as amended.

B. Applicant-Initiated Interview Summaries

Applicant would like to thank Examiner Woitach for the opportunity to have a first interview on September 29, 2022, as well as a second interview on November 2, 2022, to discuss the pending application. In accordance with MPEP § 713.04, Applicant provides below summaries of the substance of the interviews.

1. Interview on September 29, 2022

During the first interview, the pending rejections and potential amendments to the claims to overcome the pending rejections were discussed. In addition, with respect to the 35 U.S.C. 101 rejection, possible elements that would be considered under Step 2B as being unconventional were discussed, as were how the combination of steps provides for an integration and significantly more. The Examiner noted that the proposed amendments to the claims were likely to overcome the 112 rejections and the Examiner kindly agreed to review further potential amendments prior to Applicant filing the next response.

2. Interview on November 2, 2022

During the second interview, further potential amendments to the claims were discussed. The Examiner noted that the proposed amendments to the claims had the potential to overcome the remaining rejections pending additional review and searching.

Applicant would like to again thank the Examiner for his time, as well as for consideration of the proposed amendments and supporting arguments thereof.

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C. Double Patenting

Claims 10-28 are rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of co-pending Application No. 17/828,572 filed 5/31/2022 (restriction mailed 7/25/2022).

For the purposes of expediting prosecution of the present application, Applicant files herewith a Terminal Disclaimer and respectfully submits that the Office's non-statutory double patenting rejection of claims 10-28 are moot and should be withdrawn.

D. Rejection under 35 U.S.C. § 112(a)

The Office has rejected claims 10-28 under 35 U.S.C. §112(a) as allegedly failing to comply with the written description requirement. Applicant respectfully disagrees.

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended claims 10 and 11 to clarify certain elements of the claims, as suggested by the Office (see, e.g., page 7 of the most recent Office Action). Applicant submits that, in view of the amendments to claims 10 and 11, a person of ordinary skill in the art would readily understand and appreciate the elements of the claims upon review of the specification as a whole.

In view of the foregoing, Applicant respectfully submits that claims 10-28 are in compliance with 35 U.S.C. §112(a). As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112(a) be withdrawn.

E. Rejection under 35 U.S.C. § 112(b)

The Office has rejected claims 10-28 under 35 U.S.C. §112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor regards as the invention. Applicant respectfully disagrees.

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended claims 10 and 11 to clarify certain elements of the claims, as suggested by the Office (see, e.g., page 8 of the most recent Office Action). Applicant

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submits that, in view of the amendments to claims 10 and 11, the claims are not indefinite as there is no longer ambiguity as to what "different" is in reference to when the claims are read in their entirety.

In view of the foregoing, Applicant respectfully submits that claims 10-28 are in compliance with 35 U.S.C. §112(b). As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112(b) be withdrawn.

F. Rejection under 35 U.S.C. § 103

The Office maintains its rejection of claims 10-25 and rejects newly added claims 26-28 under 35 U.S.C. 103 as allegedly being unpatentable over Lo et al. (1997) ("Lo"), Benesova et al. (2013) ("Benesova"), De Mattos-Arruda et al. (2013) ("De Mattos-Arruda"), Laktionov et al. (2004) ("Laktionov"), Ellinger et al. (Urologic Oncology 29:124-129 (2011)) ("Ellinger"), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)) ("Jung"), Shaw et al. (Genome Research 22:220-231 (2012)) ("Shaw"), Lewis et al. (US 2012/0058480 Al) ("Lewis"), and Green et al. (US 2005/0260645 Al) ("Green").

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended independent claims 10 and 20 to clarify certain differences over the asserted combination of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green. Applicant submits that the claims as amended are not obvious in view of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green, because none of the references, alone or in combination, teaches or discloses all of the elements of independent claims 10 and 20.

For example, nothing in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green teaches or discloses, or even suggests, "A method of analyzing a biological sample obtained from a subject being screened for a cancer…wherein **[the] first set of sequence reads and [the] second set of sequences reads are generated using whole genome sequencing**, …**using [the] first set of sequence reads and [the] second set of sequence reads to identify mosaic variants specific to [the] tissue sample in [the] first set of sequence reads that is not present in [the] second set of sequence reads**…**identifying [the] mosaic variants specific to [the] tissue sample of [the] subject in a first additional sample of [the] subject**…

and…**providing a report based on an identification of [the] mosaic variants specific to [the] tissue sample of [the] subject in [the] first additional sample**…," as recited in claim 10 (emphasis added).

Further, nothing in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green teaches or discloses, or even suggests, "A method for early disease detection in a subject using at least two samples from the subject…wherein **[the] first set of sequence reads and [the] second set of sequence reads are generated using whole genome sequencing**…**using [the] first set of sequence reads and [the] second set of sequence reads to identify mosaic variants specific to [the] subject in [the] first set of sequence reads that is not present in [the] second set of sequence reads**…**identifying [the] mosaic variants specific to [the] subject in a second sample of [the] subject**…and…**providing a report based on an identification of [the] mosaic variants specific to [the] subject in [the] second sample**…," as recited in claim 20 (emphasis added).

In addition to the above references not disclosing all elements of the claims, the claimed invention has unexpectedly superior properties when compared to Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green. For example, the methods of the claimed invention perform a comparative analysis of the first set of sequence reads and the second set of sequence reads to identify mosaic variants that are specific to the tissue sample (claim 10) or the individual (claim 20), whereas the references cited in the Office Action merely assay a sample using a predefined panel of mutations that are agnostic to the subject being screened. As such, the claimed methods exhibit technical superiority over the cited references at least for the reason that the claimed methods have a higher sensitivity for the detection of mosaic variants (see, e.g., paragraph [0066] of the specification, as well as the exhibits that were submitted as part of the email correspondence with the Office on October 24, 2022, in conjunction with the interviews with the Examiner), facilitating an earlier detection of disease, such as, for example, cancer. The references cited in the Office Action do not contemplate performing such a comparative analysis due to the simple fact that those references are only concerned with detecting common mutations that are broadly applicable to the human population at large, resulting in a concomitant decrease in assay sensitivity.

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Further, as opposed to the methods discussed in the cited references, the claimed methods are not restricted to the identification of cancer driver genes. As discussed in claims 16 and 17, the methods of the claims allow for the detection of mosaic variants that are causal or predisposing of cancer, as well as mosaic variants that are not causal for cancer. While it is now more commonly known that mosaic variants are present in normal tissue (*see, e.g., Muyas, F., Zapata, L., Guigó, R., & Ossowski, S. (2020). The rate and spectrum of mosaic mutations during embryogenesis revealed by RNA sequencing of 49 tissues. Genome Medicine, 12(1).*), Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green failed to disclose or suggest this element, and as such, the presently claimed invention possesses superior properties over the combined teachings of these references. Similarly, it is also now more commonly known that mutations that are causal or predisposing of cancer can be present in normal tissue (*see, e.g., Yap, T. A., Ashok, A., Stoll, J., Mauer, E., Nepomuceno, V. M., Blackwell, K. L., Garber, J. E., & Meric-Bernstam, F. (2022). Prevalence of Germline Findings Among Tumors From Cancer Types Lacking Hereditary Testing Guidelines. JAMA Network Open, 5(5), Article e2213070.*). As opposed to the methods of the claims when read as a whole, the methods described in the Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green references fail to disclose or suggest the omission of mutations that are causal or predisposing of cancer when found in normal tissue as these methods are agnostic to the genetic makeup of a subject.

Claims 11-19, 26, and 28 depend from and include all of the elements of claim 10, and recite additional elements to describe embodiments of particular advantage and utility. Claims 21-25 and 27 depend from and include all of the elements of claim 20, and recite additional elements to describe embodiments of particular advantage and utility. As such, the asserted combination of Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green also fails to render the dependent claims obvious.

In view of the foregoing, Applicant submits that claims 10-28, as amended herewith, are in compliance with 35 U.S.C. § 103. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

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G. Rejection under 35 U.S.C. § 101

The Office maintains its rejection of claims 10-25 and rejects newly added claims 26-28 under 35 U.S.C. §101, because the claimed invention is allegedly directed to a judicial exception without significantly more. Applicant respectfully disagrees.

Applicant maintains the positions set forth in the response to the Final Office Action dated April 11, 2022, that the claims should be found to be subject matter eligible under Step 2A prong one (the claims are not directed to the judicial category of a mental process as the claims cannot be practically performed in one's mind), Step 2A prong two (similar to *McRO*, the methods of the present claims present improvements in the technical field of cancer diagnostics), and Step 2B (the methods of the present claims recite additional elements that amount to significantly more than any alleged judicial exception, as they recite elements that are not well-understood, routine, or conventional).

In addition to the positions asserted in response to the Final Office Action dated April 11, 2022, Applicant submits that the claims should further be found to be subject matter eligible at Step 2A prong two of the 101 analysis (as the claims present improvements in the technical field of cancer diagnostics) and Step 2B of the 101 analysis (as the claims recite still further elements that are not well-understood, routine, or conventional).

As described in further detail in response to the 103 rejection, Applicant submits that it is not well-understood, routine, or conventional to generate a first and second set of sequence reads using whole genome sequencing, identify mosaic variants specific to the tissue sample/subject in the first set of sequence reads that is not present in the second set of sequence reads, to identify the mosaic variants specific to the tissue sample/subject in a first additional sample/a second sample, and to provide a report based on the identification of the mosaic variants specific to the tissue sample/subject in the first additional sample/second sample, as recited in claims 10 and 20. Methods contemporaneous to the priority date of the application, such as, for example, those described in Lo, Benesova, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green, were predominantly focused on assaying samples of subjects using predefined panels of known mutations (generally, known cancer driver genes). As these methods were focused on the detection of known mutations using panels that were agnostic to a specific individual, such

methods would not have contemplated performing whole genome sequencing to detect mosaic variants specific to a tissue sample/subject, assaying a subsequent sample (e.g., a first additional sample, or a second sample (claims 10 and 20, respectively)) to detect a bespoke configuration of mosaic variants specific to the tissue sample/subject, and outputting a report based on the identification of such mosaic variants.

Further, as the elements of the claims that are not well-understood, routine, or conventional result in an assay that is technologically superior to contemporaneous methods (i.e., the methods of the claimed invention result in an assay with improved sensitivity to detect mosaic variants), the methods of the present claims set forth an improvement in the technical field of cancer diagnostics.

In view of the foregoing, Applicant submits that claims 10-30, as amended herewith, are in compliance with 35 U.S.C. § 101. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 101 be withdrawn.

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H. Conclusion

For at least the reasons set forth above, it is submitted that claims 10-30 are in condition for allowance. A Notice of Allowance is earnestly solicited.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

The Applicant reserves the right to pursue at a later date any previously pending or other claims that capture any subject matter supported by the present disclosure. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicant has disclaimed or disavowal any subject matter supported by the present application.

Except for issues fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees including fees due under 37 CFR § 1.16 and 1.17, which may be required, and including any required extension of time fees, or credit any overpayment to Deposit Account 15-0665 (Docket Reference: 48929.4008/US03).

Respectfully submitted,

Orrick, Herrington & Sutcliffe LLP

Dated: 11-11-2022

By: /Alex Straughn/
Alex Straughn, Reg. No. 80,155, for
Gargi Talukder, Reg. No. 61,368

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Telephone: (949) 567-6700
Facsimile: (949) 567-6710

UNITED STATES
PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/494,513	11/11/2022 04:24:49 PM ET	48929.4008/US03

Title of Invention

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8186	FILED BY	Sheila Gloss
PATENT CENTER #	61170559	AUTHORIZED BY	Alex Straughn
CUSTOMER #	182685	FILING DATE	10/05/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	John West

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 150665	E2022AAG26282989	Sheila Gloss

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	130.00	1	130.00
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
			TOTAL AMOUNT:	$300.00

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d)

and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/494,513	**11/11/2022 04:38:59 PM ET**	**48929.4008/US03**

Title of Invention

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8186	FILED BY	Sheila Gloss
PATENT CENTER #	61170903	FILING DATE	10/05/2021
CUSTOMER #	182685	FIRST NAMED INVENTOR	John West
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Alex Straughn

Documents

TOTAL DOCUMENTS: 6

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
VELCULESCU_1997_NPL.pdf	9	Non Patent Literature	3826 KB
WANG_2010_ANNOVAR_NPL.pdf	7	Non Patent Literature	262 KB
WARREN_2011_NPL.pdf	6	Non Patent Literature	816 KB
YEUNG_2013_NPL.PDF	11	Non Patent Literature	1310 KB
YI_2010_NPL.pdf	10	Non Patent Literature	1607 KB
YU_2014_NPL.pdf	7	Non Patent Literature	838 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
VELCULESCU_1997_NPL.pdf	4036846DE4F957A169D18339695E4571AB5DE2F6E6CBA0C2AC0AAD284E75E6E5AA5A7DA92ABB8A1D06A1DF610C1D034ECE1B4A8D096B407987C1CF279F6FCF22
WANG_2010_ANNOVAR_NPL.pdf	37431EFBF9FC2681F5A2F67D612D0E3874F9E06B0C3737B90FDD29C7BFDCCBD2507FFDFD22DC186B618CE78C24F7FA0AE88E7E233A5333267756A6B968F06E61
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YEUNG_2013_NPL.PDF	505C3F8A03087EA29277ADD82AAE61D09AD452D2ADAB75533DE7676E63F295427C0F3BD0C2DFCDD69445D511C11BEEBB98BCD926A9D9B74B3A2BE804C95503AA
YI_2010_NPL.pdf	33DF81E79E52596B8FD8905F3FAF16C05A5F4C64E8A80A372C7CACF85C812B86D80429113834312 4FFCA0F529413F0DC686B2DD1E033084FDCDCCD98793DACE6
YU_2014_NPL.pdf	788DB7F3971B24E3F440FD129E4E1FAB0A145EB12CD6DF1000E40FFB048207AA96F592FD805801AC251D0A4B97D4FA203DE3B6EDC0EFAA985C826D5D717C64E0

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New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/494,513	Filing Date 10/05/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	11/11/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 20	= 1		x $50 =	50
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	50

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	Examiner
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/PATRICIA A VOLPE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 11/07/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1672	

NOTIFICATION DATE	DELIVERY MODE
11/07/2022	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
jmichel@orrick.com
vsantos@orrick.com

Foresight EX1108-p. 147
Foresight v Personalis
IPR2024-00170

Applicant-Initiated Interview Summary	**Application No.** 17/494,513	**Applicant(s)** West, John		
	Examiner Joseph T Woitach	**Art Unit** 1672	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 2

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
Joseph T Woitach	Primary Examiner	Video Conference
Alex Straughn	Attorney	
Gargi Talukder	Attorney	
Leslie Grab	Attorney	

Date of Interview: 02 November 2022

Issues Discussed:

35 U.S.C. 101

The basis and requirements of the claim were discussed, and how the combination of steps were not conventional in view of the art of record and the analysis of cancer samples using panels of correlated known gene variants, and provided significantly more when viewed as a whole.

35 U.S.C. 103

The combination of steps were discussed in view of the art of record and potential art relative to 'plurality' of variants used in the analysis. It was agreed that plurality was not necessary, and that the combination of steps and limitations appeared to provide unexpected ability to better detect various cancer types especially in the context of personalized element of the variants obtained from practicing the first step of the claims.

Proposed Amendment(s)

The support and necessity of the limitation "plurality" was discussed in addressing the rejections of record. It was generally agreed that the limitation was not necessary, and would be deleted.

/Joseph Woitach/ Primary Examiner, Art Unit 1672	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Applicant-Initiated Interview Summary	**Application No.** 17/494,513	**Applicant(s)** West, John		
	Examiner Joseph T Woitach	**Art Unit** 1672	**AIA (First Inventor to File) Status** Yes	**Page** **2 of 2**

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Foresight EX1108-p. 149
Foresight v Personalis
IPR2024-00170

From: Straughn, Alex
To: Woitach, Joseph
Cc: Talukder, Gargi
Subject: Application # 17/494,513 - Proposed Amendments to the Claims | Attorney Docket # 48929.4008/US03
Date: Friday, October 28, 2022 1:31:23 PM
Attachments: image002.png

CAUTION: This email has originated from a source outside of USPTO. **PLEASE CONSIDER THE SOURCE** before responding, clicking on links, or opening attachments.

Dear Examiner Woitach,

We are writing you in regards to application # 17/494,513. We appreciate having the opportunity to further discuss the pending application with you on November 2, 2022. During our meeting, we would like to discuss further proposed amendments to the claims in view of our prior discussion. Provided below is a mock-up of further potential amendments to the first independent claim (indicated by the yellow highlights), as well as a couple of new dependent claims.

We look forward to speaking with you next week.

All the best,
Alex Straughn

10. (Currently amended) A method of analyzing a biological sample obtained from a subject being screened for a cancer, wherein the biological sample is from a non-fetal source, the method comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, and wherein (i) said first set of nucleic acid molecules is extracted from tissue sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a blood sample;

(b) using said first set of sequence reads and said second set of sequence reads to identify ~~one or more~~ a first plurality of mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(c) subsequent to (b), identifying said ~~one or more~~ first plurality of mosaic variants specific to said tissue sample of said subject in a first additional sample of said

subject, wherein said first additional sample is obtained from a source that is different than said tissue sample and at a time point that is different than said tissue sample; and

(d) providing a report based on an identification of said ~~one or more~~ first plurality of mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said subject.

29. (New) The method of claim 10, wherein said first plurality of mosaic variants specific to said tissue sample comprises ### or more mosaic variants.

30. (New) The method of claim 11, wherein said second plurality of mosaic variants specific to said tissue sample comprises ### or more mosaic variants.

Alex R. Straughn
Patent Agent

Orrick
Houston
T +17136586427
M +15028511800
astraughn@orrick.com

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USPTO Automated Interview Request (AIR)

Oct 26 2022

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Gargi Talukder, Alex Straughn, Leslie Grab

S-signature:
/Alex Straughn/

Registration Number:
80155

U.S. Application Number:
17494513

Confirmation Number:
8186

E-mail Address:
astraughn@orrick.com

Phone Number:
+1 5028511800

Proposed Time of Interview:
11-2-2022 11:00 AM ET

Alternative Proposed Time(s) of Interview:
11-2-2022 12:00 PM ET

Alternative Proposed Time(s) of Interview:
11-3-2022 12:00 PM ET

Prefered Interview Type:
Video Conference

I am the applicant or applicant's representative for this application.

Topic for Discussion:
Discuss rejections in above case.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 10/24/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1672	

NOTIFICATION DATE	DELIVERY MODE
10/24/2022	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
jmichel@orrick.com
vsantos@orrick.com

Foresight EX1108-p. 153
Foresight v Personalis
IPR2024-00170

Examiner-Initiated Interview Summary	**Application No.** 17/494,513	**Applicant(s)** West, John		
	Examiner Joseph T Woitach	**Art Unit** 1672	**AIA (First Inventor to File) Status** Yes	**Page** **1 of 2**

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
Joseph T Woitach	Primary Examiner	Telephonic
Alex Straughn	Attorney	

Date of Interview: 19 October 2022

Issues Discussed:

35 U.S.C. 101

It was indicated that for the 101, I think addressing the above will address my concerns for 101. See attached email.

35 U.S.C. 103

The limitation for step b) and needing 'one or more' appears to be an issue for overcoming the 103. As amended:
"(b) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;"
and from our discussions and additional evidence, it appeared that the power of the method and of detection was in the use of a lot of mosaic variants or as many as possible mosaic variants that were observed in a)-b) and as amended when using whole genome analysis. It appears that the teaching of Benesova et al for use tumor specific mutations in the primary tumor (on page 230 2nd paragraph, first column) provides for identifying and using one or more. Possibly to be consistent with unexpected ability/ properties/outcomes provided in the evidence, the claims would need to be consistent with what data was being evaluated and used to arrive at the evidence.

/Joseph Woitach/ Primary Examiner, Art Unit 1672	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general

indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Foresight EX1108-p. 155
Foresight v Personalis
IPR2024-00170



NeXT Personal™

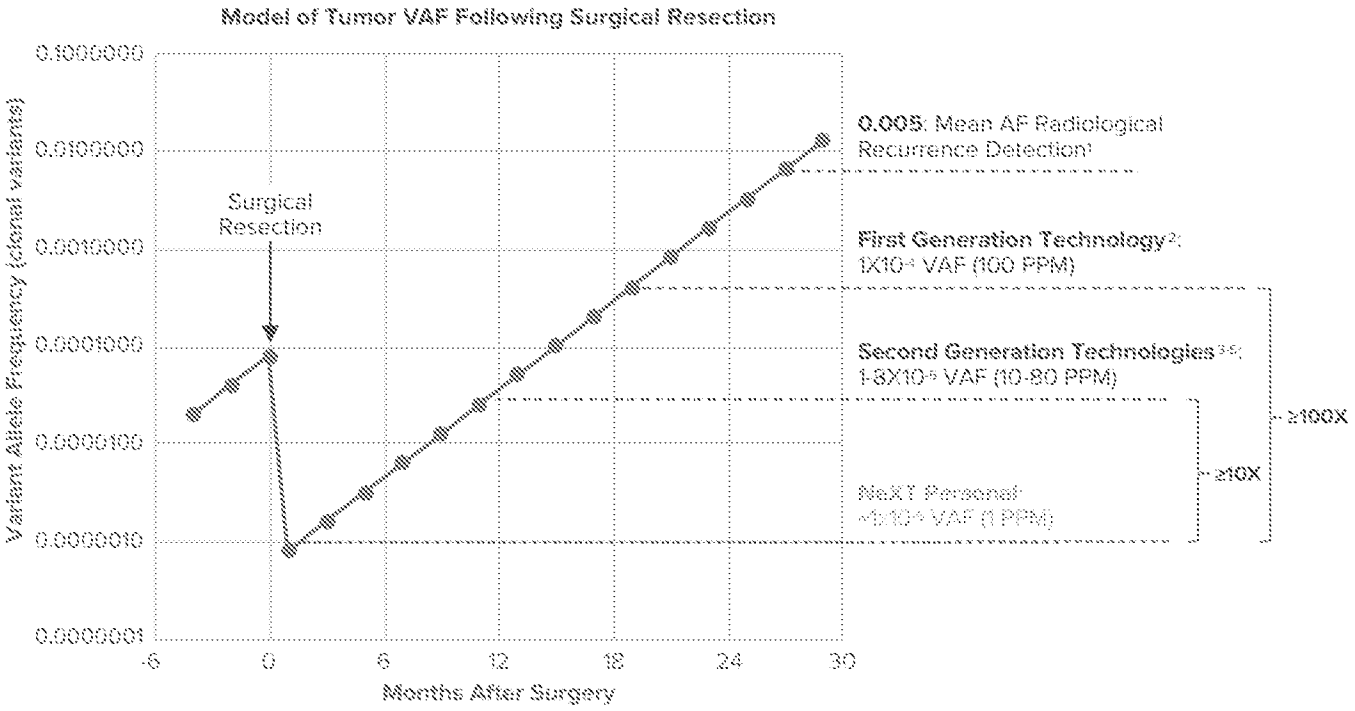
The Next Generation in Molecular Residual Disease Testing and Variant Monitoring for Solid Tumors

Personalis®

Delivering Industry-Leading Sensitivity to Detect Residual Disease at the Earliest Timepoints

NeXT Personal, an advanced, personalized, and tumor-informed liquid biopsy assay, is designed to detect molecular residual disease (MRD) and cancer recurrence at the earliest timepoints — prior to, during or after treatment — in patients previously diagnosed with cancer. While circulating tumor-derived DNA (ctDNA) is an emerging biomarker for many cancers, the limited sensitivity of current detection methods reduces its utility for diagnosing MRD across a variety of clinical applications. Standard-of-care (SOC) radiological-based technologies, including CT, PET and MRI scans, also remain limited in their ability to detect residual disease during or after surgical or systemic therapy due to the minimum tumor volume required.[1] Therefore reliable, sensitive detection and quantification of MRD remains a key challenge, particularly in early-stage cancers, where timely detection of small micrometastatic lesions may enable treatment that prevents progression to advanced metastatic, incurable disease. To address these challenges, NeXT Personal was developed to deliver industry-leading MRD sensitivity in the range of 1-3 parts per million (PPM) representing a 10-100X increase over other available methods (Figure 1), while requiring only a single tube of blood (4mL plasma/15ng cfDNA), and 1mm^2 of FFPE tumor tissue.

Figure 1: MRD Sensitivity: Targeting Detection at Earliest Timepoints



Model Assumptions: Median breast tumor size detected by mammography: 1.3cm, Median shedding per NSCLC TRACERx study[6]; Residual tumor from surgery: 1%; Volume doubling time (actual VAF time): 2 months

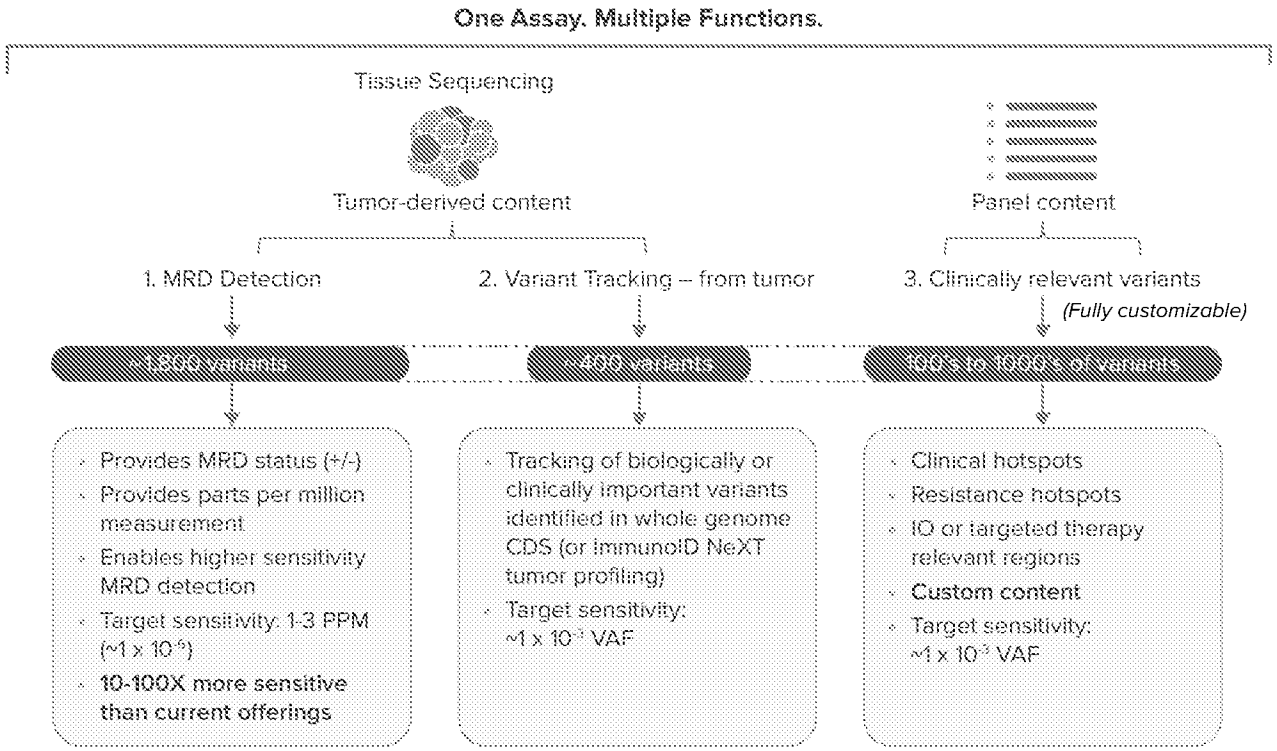
In the biopharma setting, MRD is rapidly emerging as a key biomarker in therapy development, whereby more sensitive detection and quantification of MRD may provide substantial benefits versus less sensitive methods through the reduction of false negative detection of cancer. These benefits include:

- More efficient cohort enrichment of study participants that are MRD positive.
- Faster time to surrogate endpoint analysis through earlier detection of MRD.
- Enhanced accuracy of recurrence and survival risk.
- Greater resolution of therapy response.

Unique Assay Design Provides Unprecedented Insights Into Longitudinal Disease Monitoring

While the MRD component of NeXT Personal provides a highly sensitive and aggregated measurement of tumor burden in plasma, the ability to simultaneously track individual variants longitudinally can also be utilized to further our understanding of tumor biology and its dynamic response to therapy. Therefore, in addition to MRD, NeXT Personal provides the ability to track and annotate individual variants over the whole evolution of a cancer patient's trajectory in a single panel design. Variants tracked by NeXT Personal in the blood are derived from those detected in the tissue, as well as those specified for panel inclusion by the user (Figure 2).

Figure 2: NeXT Personal Assay Features: Advanced, higher sensitivity, personalized, tumor-informed liquid biopsy for MRD & Variant Tracking



For every panel, NeXT Personal boasts the capacity to include up to 400 single nucleotide variants (SNVs) detected in the tumor to track in plasma. NeXT Personal automatically filters for variants that lie in coding regions of clinically relevant genes, prioritizing those in genes with known relevance to cancer. This ensures that the most biologically and clinically important variants are tracked longitudinally to deliver insights on evolving tumor biology (Figure 2.2).

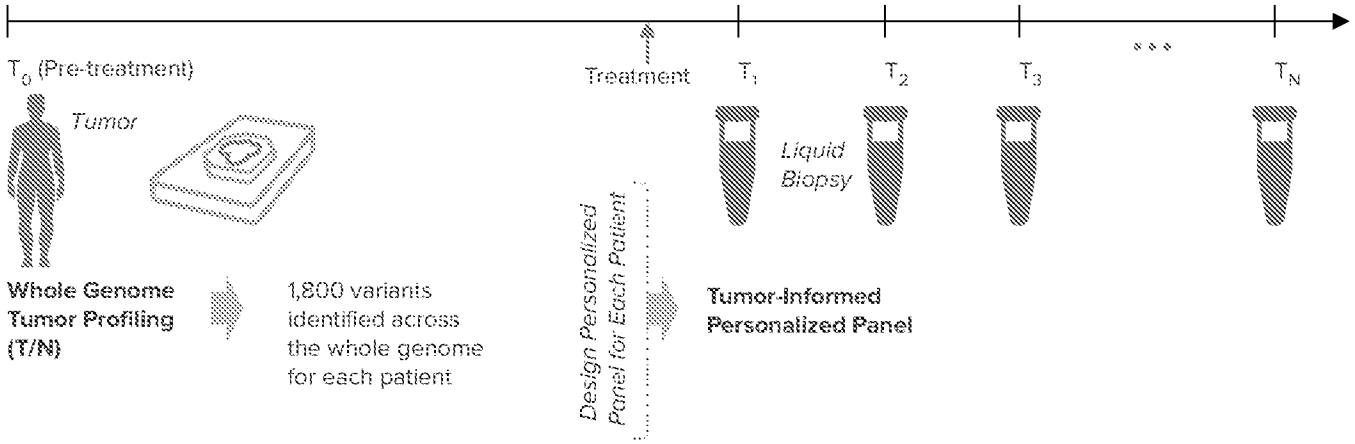
Similarly, variants not detected in the tumor may also be added during the panel design process. As custom content, users may define their own set of variants that may be representative of known clinical hotspots (ex. EGFR T790M), resistance hotspots, driver mutations (which may allow detection of a second primary tumor), or other therapy-specific and biologically important variants studied or monitored in clinical research. Capacity for user-supplied content can include up to thousands of variants. Alternatively, users may also leverage clinically relevant content developed and curated by Personalis in addition to, or instead of, user-supplied content (Figure 2.3).

Target sensitivity for individual variant detection is 0.1% VAF.

Leveraging Tissue-Based Whole Genome Sequencing (WGS) Yields Best-In-Class MRD Performance in Plasma: 1-3 PPM Sensitivity

Central to the MRD performance of NeXT Personal is the number of tumor-derived mutations interrogated in patient plasma samples. Analytical and clinical MRD sensitivity can be increased by expanding coverage of loci containing tumor-specific mutations.[7] To this end, NeXT Personal leverages the broad array of SNVs detected with >30x WGS coverage of a patient's tumor (and accompanying normal) to inform the selection of 1,800 SNVs for inclusion in a personalized MRD panel (Figure 3). The majority of these patient-specific SNVs are located in non-coding regions of the genome. Finally, Personalis' extensive investment into the Illumina® NovaSeq® series enables ultra-deep sequencing (~100,000 raw depth), while keeping costs in line with other MRD tests that interrogate many fewer loci.

Figure 3: NeXT Personal: Advanced, Higher Sensitivity, Personalized, Tumor-Informed Liquid Biopsy for MRD & Variant Tracking



Upon completion of sequencing with the tumor-informed personalized panel, data generated across these 1,800 targeted loci are analyzed and an aggregated measurement of tumor burden is reported in a PPM readout with accompanying MRD status (MRD+/-). Rather than using a predetermined minimum number of mutations to define MRD status, NeXT Personal uses advanced, proprietary statistical analyses to distinguish signal from noise for each individual patient panel and sample. Guided by a P-value threshold of <0.001 (derived from a specificity target of >99.9%), NeXT Personal is optimized for both sensitivity and specificity.

Assessing the prospective utility of individual MRD targets is an important aspect of tumor-informed panel design. Tissue WGS often yields tens of thousands of mutations, but selecting those that are most likely to be (1) shed into the blood and (2) have high signal-to-noise profiles is of critical importance. While the human genome harbors a plethora of inherently noisy regions, Personalis, leveraging its extensive experience with WGS, is the first company to develop methods to filter for targets that may be difficult to resolve if detected in plasma. Further, the abundance of variants identified via WGS allows the selection of predominately truncal mutations with high allele frequencies; those that are more likely to be shed into the blood.

The powerful combination of WGS to enable target breadth, coupled with robust error and noise reduction methods, results in MRD sensitivity in the 1-3 PPM range with ≥99.9% specificity (Figures 4 and 5).

Figure 4: Cell line dilution series, HCC38, demonstrates the linearity of tumor signal across the dilution series down to the 1-3PPM range (C50 and C95, respectively). Orthogonal confirmation using droplet digital PCR (ddPCR) demonstrates near-perfect concordance down to ddPCR LOD (750 PPM).

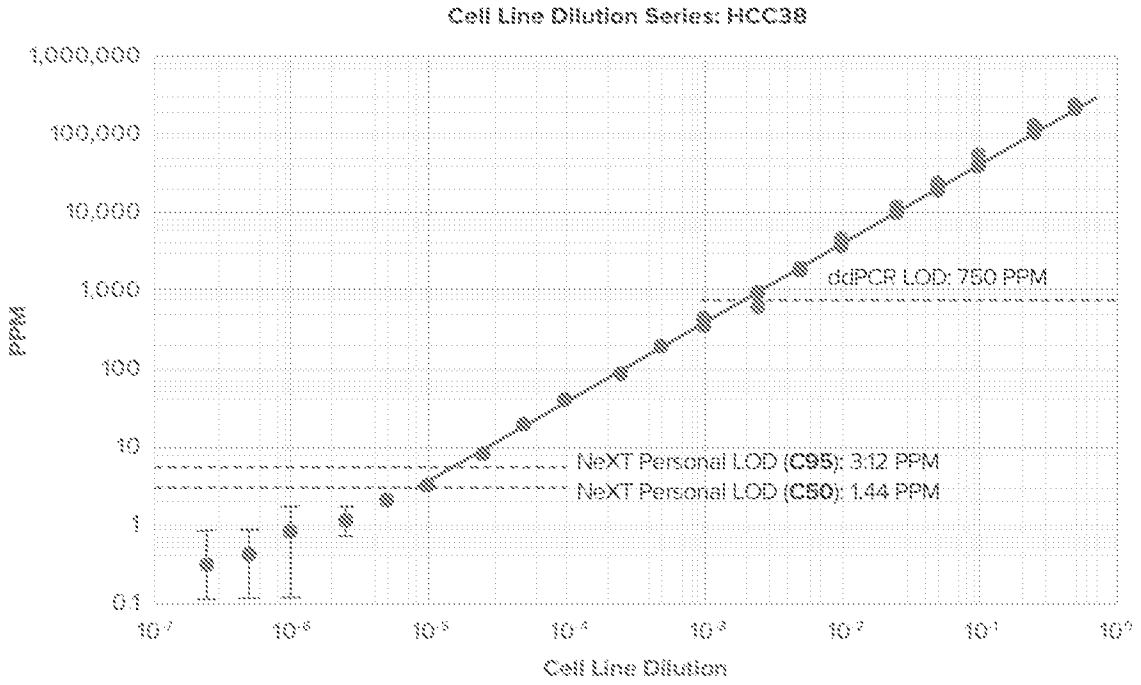
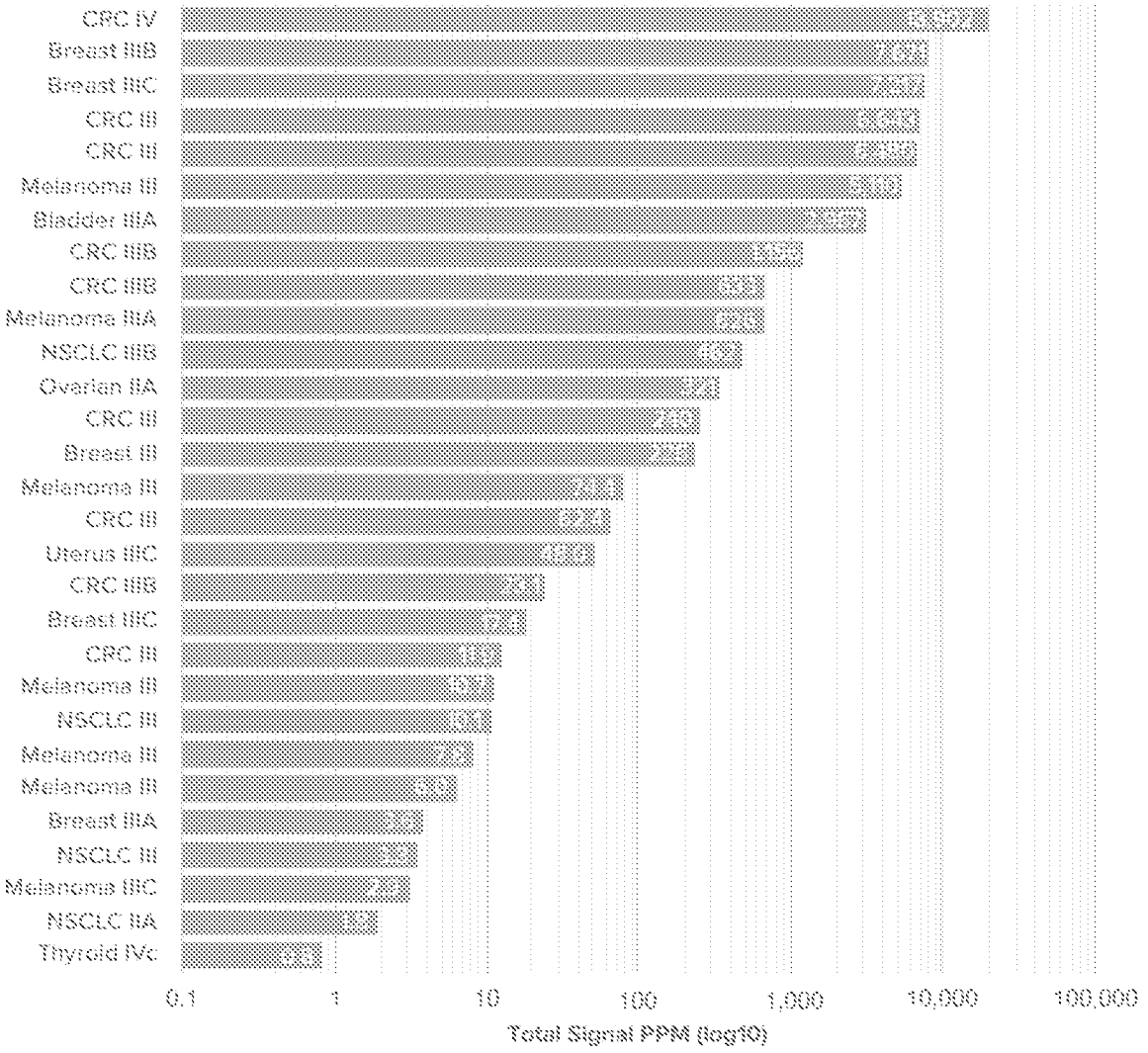


Figure 8: Patient T/N/P trios across 8 tumor types and 3 stages were sequenced demonstrating range of detection, 0.8 – ~19,000 PPM



Target Breadth Mitigates Challenging Sample Conditions

Target breadth is important to achieve higher sensitivity, but it is also important to overcome challenging sample conditions.The success of tumor-informed liquid biopsy approaches is dependent on the number of targeted mutant fragments present in the sample. Key variables that determine successful MRD detection are: (1) number of genomic equivalents (GEs) in the plasma sample, (2) tumor fraction in the plasma sample, and (3) tumor mutational burden (TMB) in the tissue sample. Under ideal sample conditions — characterized by a high number of GEs in plasma, a high tumor fraction in plasma, and a high TMB in tissue — narrower tumor-informed panel footprints (ex. those constrained by the tissue exome-seq) and fixed content panels may be sufficient to detect MRD.

However, ideal sample conditions are often not attainable:

- Tumor fraction in plasma in early-stage cancers is often low due to limited shedding of DNA molecules from small, localized lesions.[8]
- Plasma volume can be difficult to obtain due to patient variability, study design, and other blood analyte testing requirements.
- Finally, tissue TMB is highly variable and less dependent on tumor type and tumor stage[9], with low TMB tumors reducing the number of high-quality variant candidates for MRD panel inclusion, materially impacting assay performance.

NeXT Personal mitigates these challenges by ensuring high coverage (1,800 loci) of the tumor-derived DNA molecules, increasing the detection probability of mutant fragments even when there are few. Therefore, even in challenging sample conditions, NeXT Personal is able to deliver superior assay performance.

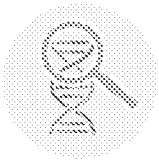
Combining ImmunoID NeXT™ and NeXT Personal Yields Multidimensional View Into Tumor Biology

In addition to NeXT Personal, Personalis' flagship tissue-based immunogenomics platform, ImmunoID NeXT, may also be run from the same tissue sample with no additional tumor material required. For the first time, investigators can comprehensively characterize both the tumor- and immune-related components of the tumor microenvironment while still retaining the ability to longitudinally monitor MRD and variants in the blood with industry-leading sensitivity, even in sample-limited scenarios.

Table 1

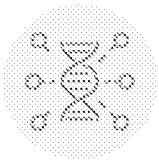
Key NeXT Personal Specifications		
General	Cancer Stage	All
	Cancer Type	Solid tumors
	cfDNA input	15 ng
	Blood / Plasma Volume	10 mL (1 tube) / 4 mL
	Assay Type	Tumor-informed
	Front-End Tissue Sequencing	WGS
	Tissue Sequencing Coverage	>30X
	Plasma Sequencing	Targeted panel
	Plasma Sequencing Coverage	~100,000X (raw)
	Assay Multifunctionality	1. MRD 2. Tumor variant tracking 3. Customer-specified variant tracking
MRD	# MRD targets	1,800
	Analytical Sensitivity	1-3 PPM
	Analytical Specificity	≥99.9%
Tumor Variant Tracking	Variant capacity	400
	Source of variants	Coding regions only
	Analytical Sensitivity	0.1% VAF
Panel Variant Tracking	Variant capacity	1,000's
	Source of variants	Custom / Customer specified
	Analytical Sensitivity	0.1% VAF

Unique Features of NeXT Personal



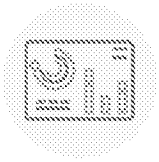
Deep Sequencing

~100,000X raw coverage for plasma is performed across 1,800 loci, enabling sequencing dollars to be directed to variants of highest value. >30X WGS coverage for tumor and normal tissue is performed to detect SNVs for targeted panel inclusion.



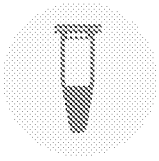
Industry Leading MRD Performance

1-3 PPM MRD LOD is 10-100X more analytically sensitive than other MRD solutions on the market, aiding the detection of MRD and recurrence at the earliest timepoints. ≥99.9% specificity minimizes the rate of false positive results.



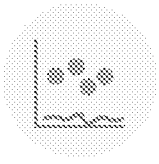
Assay Multifunctionality

NeXT Personal is not just an MRD solution. In addition to MRD, NeXT Personal tracks and annotates individual variants — those that are detected in the tumor, and those specified for panel inclusion by the user — to advance knowledge of tumor biology and observe emergence of known clinical and resistance hotspots.



Low Input Sample Requirements

NeXT Personal requires only 15ng of cfDNA, or 1 tube of blood (4mL of plasma), to deliver exceptional performance. Additionally, Personalis' protocols enable flexible sample formats — blood, plasma, and cfDNA — to be processed in the lab. Additionally, as little as 1mm^3 of FFPE tumor tissue is required for WGS.



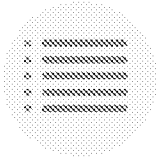
Advanced Error Suppression

Robust, proprietary error suppression techniques reduce the error rate from sequencing, PCR and other sample processing steps.



Panel Identification

Included in every NeXT Personal design, Personalis deploys a SNP-based quality control measure to ensure a patient's panel is never mixed with another patient's sample.



Personalis-Provided Panel Content

Personalis provides the option to include a carefully curated list of clinically actionable and resistance hotspots in addition to or in the absence of panel content specified by the user.

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3. Genome-wide circulating tumor DNA monitoring for bladder cancer treatment management and organ preservation. Nordentoft *et al.*, ASCO 2021, Abstract e16527
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9. Pan cancer analysis of whole genomes. Campbell *et al.*, Nature, 2020

Sales Contact

United States
info@personalis.com

Europe
europe@personalis.com

Other Countries
info@personalis.com

Personalis, Inc.

1330 O'Brien Drive, Menlo Park, CA 94025
+1 855 GENOME4 (436-6634) | +1 650 752-1300
www.personalis.com

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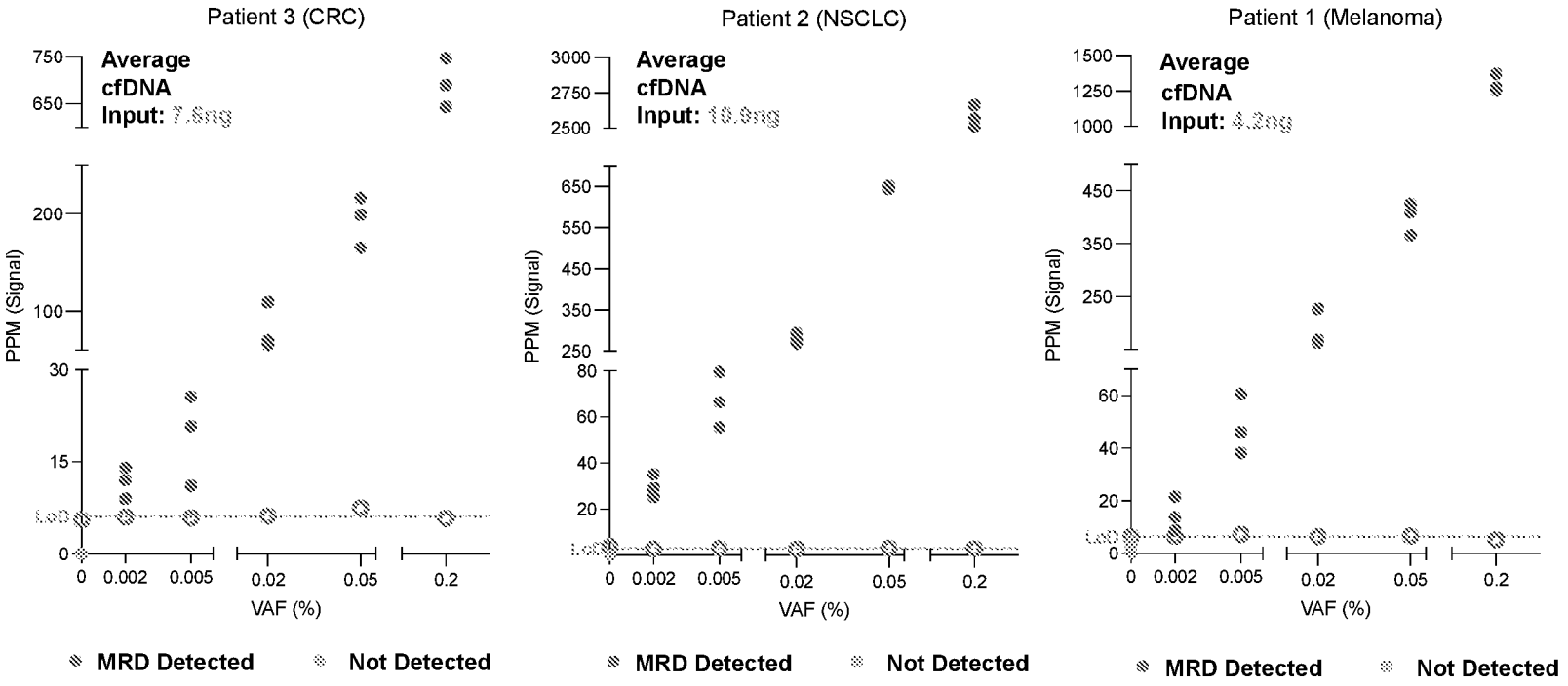
Blinded dilution study demonstrates 100% sensitivity & 100% specificity

Blinded AF% - Dilution Series	Patient Set 1				Patient Set 2				Patient Set 3			
	LOD	PPM (Signal)	P-value	MRD Call	LOD	PPM (Signal)	P-value	MRD Call	LOD	PPM (Signal)	P-value	MRD Call
0.20%	5.4	1372.3	0	Detected	2.8	2662.3	0	Detected	4.9	747.4	0	Detected
0.20%	4.7	1274.2	0	Detected	2.6	2568	0	Detected	5.1	690	0	Detected
0.20%	5.4	1252.2	0	Detected	2.9	2512.1	0	Detected	7.3	643.8	0	Detected
0.05%	6.8	425.6	0	Detected	3.1	651.4	0	Detected	8.2	216.2	0	Detected
0.05%	6.3	409.5	0	Detected	2.8	647.2	0	Detected	5.9	199.2	0	Detected
0.05%	7	365.6	0	Detected	3	644.4	0	Detected	8.3	165.3	0	Detected
0.02%	6.3	227.1	0	Detected	2.5	294	0	Detected	6.4	109.4	0	Detected
0.02%	6.3	168.1	0	Detected	2.7	278.8	0	Detected	5	70	0	Detected
0.02%	6.8	163	0	Detected	2.7	268.7	0	Detected	7	65.6	0	Detected
0.005%	7.6	60.6	0	Detected	3	79.4	0	Detected	7.7	25.6	0	Detected
0.005%	5.8	46.1	0	Detected	2.8	66.4	0	Detected	5.7	20.8	0	Detected
0.005%	8.2	38.2	0	Detected	2.9	55.5	0	Detected	4.1	11.1	0	Detected
0.002%	6.5	21.6	0	Detected	2.8	35	0	Detected	7.2	12	0	Detected
0.002%	6.8	13.7	0	Detected	2.5	29	0	Detected	5.3	14	0	Detected
0.002%	6.6	8.8	2.00E-05	Detected	2.8	25.3	0	Detected	5.4	9	1.00E-06	Detected
WT	4.4	4.4	0.001687	Not Detected	3.3	0	1	Not Detected	4	0	1	Not Detected
WT	8.9	3	0.107785	Not Detected	3.7	0	1	Not Detected	8.2	0	1	Not Detected
WT	6.2	0	1	Not Detected	4.4	0	1	Not Detected	4.4	0	1	Not Detected
	Average cfDNA input: 4.2ng				Average cfDNA input: 10.9ng				Average cfDNA input: 7.6ng			

- Demonstrates **100% sensitivity** to the **lowest dilution (0.002% : 20 PPM)**
- **100% specificity** in wild type samples

Confidential and Proprietary

100% sensitivity & 100% specificity achieved in customer blinded study



Confidential and Proprietary

From: Woitach, Joseph
To: Straughn, Alex
Cc: Talukder, Gargi; Woitach, Joseph
Subject: RE: Application # 17/494,512 - Proposed Amendments to the Claims | Attorney Docket # 48929.4008/US03
Date: Wednesday, October 19, 2022 12:55:29 PM
Attachments: image003.png

Hello Mr Straughn,

The proposed amendments look like they do not raise new 112 issues, but I am not sure they are sufficient to address the 103, and still thinking about the 101. The issue is for step b) and needing 'one or more'.

"(b) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;"

From our discussions, it appeared that the power of the method and of detection was in the use of a lot of mosaic variants or as many as possible mosaic variants that were observed in a)-b) whole genome analysis. I think the teaching of Benesova et al for use tumor specific mutations in the primary tumor (on page 230 2nd paragraph, first column) provides for identifying and using one or more. I think to be consistent with unexpected ability/properties/outcomes provided in the other documents, the claims would need to be consistent with what data was being evaluated and used to arrive at the evidence.

I have not looked at the specification for types of support, but willing to evaluate any threshold value or threshold descriptive number of mosaic variants that achieve the greater level of detection, and/or a further discussion for something I am missing.

For the 101, I think addressing the above will address my concerns for 101.

Let me know a time if you would like to discuss this further.

Regards,

Joe

From: Straughn, Alex <astraughn@orrick.com>
Sent: Wednesday, October 19, 2022 10:50 AM
To: Woitach, Joseph <Joseph.Woitach@USPTO.GOV>
Cc: Talukder, Gargi <gtalukder@orrick.com>
Subject: Application # 17/494,512 - Proposed Amendments to the Claims | Attorney Docket # 48929.4008/US03

CAUTION: This email has originated from a source outside of USPTO. **PLEASE CONSIDER THE SOURCE** before responding, clicking on links, or opening attachments.

Dear Examiner Woitach,

We are writing you in regards to application # 17/494,512. First, thank you again for the great conversation on September 29, 2022. We appreciate having the opportunity to discuss the pending application with you. During the interview, you were kind enough to offer to review proposed amendments to the claims prior to submission in a response to office action.

The proposed amendments to the claims are in the attached document and are indicated by a yellow highlight, and we have also included notes in the text indicating exemplary areas for where the proposed amendments can find basis in the specification.

As we also discussed during our Interview, please find attached a copy of some data and a brochure from the assignee of this application.

After you have had an opportunity to review, we would be happy to have another conversation regarding the pending application.

All the best,
Alex Straughn

Alex R. Straughn
Patent Agent

Orrick
Houston
T +17136586427
M +15028511800
astraughn@orrick.com

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CLAIMS

1-9. (Canceled)

10. (Currently amended) A method of analyzing a biological sample obtained from a subject being screened for a cancer, wherein the biological sample is from a non-fetal source, the method comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, and wherein (i) said first set of nucleic acid molecules is extracted from tissue sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a blood sample;

(b) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(c) subsequent to (b), identifying said one or more first mosaic variants specific to said tissue sample of said subject in a first additional sample of said subject, wherein said first additional sample is obtained from a source that is different than said tissue sample and at a time point that is different than said tissue sample; and

(d) providing a report based on an identification of said one or more first mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said subject.

Commented [SA1]: [0076] The methods as disclosed herein may comprise using whole genome sequencing. In some cases, the whole genome sequencing is used to identify mosaic variants in a person.

11. (Currently amended) The method of claim 10, further comprising identifying one or more second mosaic variants specific to said tissue sample of said subject in a second additional sample of said subject, wherein said second additional sample comprises distal nucleic acids transported in the form of cell-free DNA, which second additional sample is obtained ~~from a source or~~ at a time point that is different than said tissue sample and said first additional sample.

12. (Previously presented) The method of claim 10, further comprising providing a recommendation for a therapeutic intervention based on an identification of said one or more first mosaic variants specific to said tissue sample of said subject.

13. (Previously presented) The method of claim 10, wherein said tissue sample comprises a metastatic tissue sample, a mixed tissue sample, a biopsy, or a core needle biopsy.

14. (Previously presented) The method of claim 11, wherein said first and/or second additional sample comprises a blood sample, a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.

15. (Previously presented) The method of claim 11, wherein said one or more first and/or second mosaic variants specific to said tissue sample of said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

16. (Previously presented) The method of claim 11, wherein said one or more first and/or second mosaic variants specific to said tissue sample of said subject are causal or predisposing for a cancer.

17. (Previously presented) The method of claim 11, wherein said one or more first and/or second mosaic variants specific to said tissue sample of said subject are non-causal for a cancer.

Commented [SA2]: [0070] ... In some cases, one or more samples may be obtained in the subject's life.

[0170] The methods disclosed herein may comprise obtaining a sample from a subject, such as a human subject. ... In some cases, the methods may comprise obtaining distal nucleic acids from multiple sources. The methods disclosed herein may comprise specifically detecting, profiling, or quantitating molecules (e.g., nucleic acids, DNA, RNA, etc.) that are within the biological samples.

[0171] One or more nucleic acids may be isolated from one or more sources. For example, DNA is isolated from one or more sources. In some cases, the sample may be distal nucleic acids obtained from intact cells being transported from their original location. ... In another example, circulating tumor cells can lead to metastases in cancer.

[0172] In some cases, the sample may be distal nucleic acids obtained from dead cells. ... For example, the sample may be distal nucleic acids transported in the form of cell-free DNA (cfDNA). In other cases, the sample may be distal nucleic acids transported in the form of cell-surface-bound DNA (csbDNA). The sample may be distal nucleic acids found in bodily fluids.

18. (Previously presented) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, first additional sample, or second additional sample.

19. (Previously presented) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, first additional sample, or second additional sample.

20. (Currently amended) A method for early disease detection in a subject using at least two samples from the subject, wherein the at least two samples are from a non-fetal source, said method comprising:

(a) obtaining a blood sample from said subject;

(b) extracting (i) a first set of nucleic acid molecules from a first component separated from a blood sample of said subject and (ii) a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample;

(c) quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules present in said first component separated from a blood sample;

(d) comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity;

(e) if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads generated by sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules, wherein said first set of sequence reads and said second set of sequence reads are generated using whole genome sequencing, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules;

Commented [SA3]: [0076] The methods as disclosed herein may comprise using whole genome sequencing. In some cases, the whole genome sequencing is used to identify mosaic variants in a person.

(f) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(g) subsequent to (f), identifying said one or more first mosaic variants specific to said subject in a second sample of said subject, which second sample is obtained ~~from a source or~~ at a time point that is different than said blood sample; and

(h) providing a report based on an identification of said one or more first mosaic variants specific to said subject in said second sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in said subject.

21. (Previously presented) The method of claim 20, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

22. (Currently amended) The method of claim 20, further comprising identifying one or more second mosaic variants specific to said subject in a third sample of said subject, which third sample is obtained ~~from a source or~~ at a time point that is different than said blood sample and said second sample.

23. (Currently amended) The method of claim 22, wherein said second or third sample comprises a blood sample, ~~a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy,~~ a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample of said subject.

24. (Previously presented) The method of claim 20, further comprising providing a recommendation for a therapeutic intervention based on an identification of said one or more first mosaic variants specific to said subject.

25. (Previously presented) The method of claim 22 wherein said one or more first and/or second mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

26. (Previously presented) The method of claim 10, wherein said one or more first mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

27. (Previously presented) The method of claim 20, wherein said one or more first mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

28. (Previously presented) The method of claim 10, wherein said predicting, diagnosing, and/or prognosing of (d) comprises one or more of the following: (i) diagnosing a cancer, (ii) identifying a cancer, (iii) determining a stage of a cancer, (iv) assessing risk of a cancer, (v) assessing risk of cancer recurrence, (vi) assessing reproductive risk, (vii) assessing efficacy of a drug, (viii) assessing risk of an adverse drug reaction, (ix) predicting optimal drug dosage, (x) predicting drug resistance, or any combination thereof.

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17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 10/05/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	

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1672	

NOTIFICATION DATE	DELIVERY MODE
10/05/2022	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
jmichel@orrick.com
vsantos@orrick.com

Foresight EX1108-p. 177
Foresight v Personalis
IPR2024-00170

Applicant-Initiated Interview Summary	**Application No.** 17/494,513	**Applicant(s)** West, John		
	Examiner Joseph T Woitach	**Art Unit** 1631	**AIA (First Inventor to File) Status** Yes	**Page** **1 of 2**

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
Joseph T Woitach	Primary Examiner	Video Conference
Gargi Talukder	Attorney	
Alex Straughn	Attorney	
Leslie Grab	Attorney	

Date of Interview: 29 September 2022

Issues Discussed:

35 U.S.C. 101

Possible elements under Step 2B were discussed as possibly unconventional, and how the combination of steps provides for an integration and significantly more.

35 U.S.C. 112

Limitations for the 101 and 103 were generally evaluated to resolve the 112. Examiner agreed to review potential amendments prior to filing the next response for further discussion.

35 U.S.C. 103

Possible limitations and arguments that are not taught in the cited references and not obvious were discussed, as well as possible evidence for greater personalization and accuracy of the method.

/Joseph Woitach/ Primary Examiner, Art Unit 1631	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

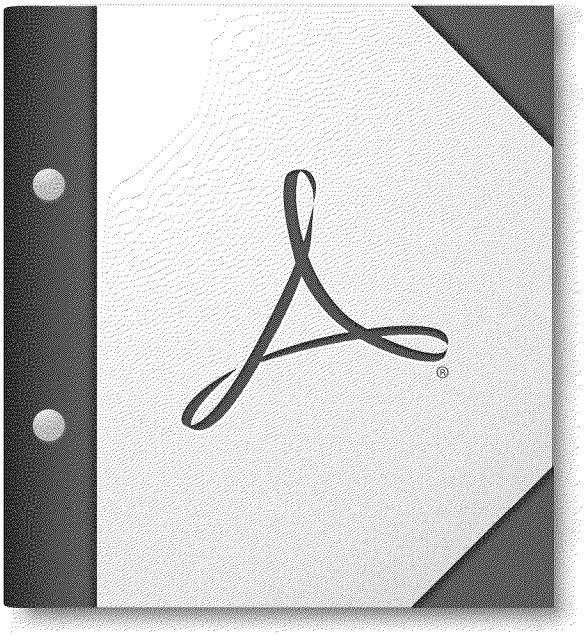
Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general

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indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Sep 13 2022

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Gargi Talukder, Alex Straughn, Leslie Grab

S-signature:
/Alex Straughn/

Registration Number:
80155

U.S. Application Number:
17494513

Confirmation Number:
8186

E-mail Address:
astraughn@orrick.com

Phone Number:
+1 5028511800

Proposed Time of Interview:
9-29-2022 2:00 PM ET

Alternative Proposed Time(s) of Interview:
10-4-2022 1:00 PM ET

Alternative Proposed Time(s) of Interview:
10-11-2022 12:00 PM ET

Prefered Interview Type:
Video Conference

I am the applicant or applicant's representative for this application.

Topic for Discussion:
Discuss rejections in above case; if there is time remaining, discuss rejections in co-pending applications 17748200 (conf. # 2190) and 17828572 (conf. # 4109)

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 08/29/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
08/29/2022	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
jmichel@orrick.com
vsantos@orrick.com

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IPR2024-00170

Office Action Summary	Application No. 17/494,513	Applicant(s) West, John	
	Examiner Joseph T Woitach	Art Unit 1631	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 8/4/2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 10-28 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) 10-28 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

RCE TrackOne Request

Applicants request filed 8/4/2022 has been granted (see paper mailed 8/12/2022).

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/4/2022 has been entered.

Applicant's Amendment

Applicant's amendment filed 8/4/2022 has been received and entered. Claims 10-20, 22-25 have been amended, claims 1-9 have been cancelled and claims 26-28 have been added.

Claims 10-28 are pending.

Election/Restriction

Applicant's election without traverse of Group II, and the species of a blood sample and SNPs in the reply filed on 2/9/2022 was acknowledged. Upon search and review of the

specification it did not appear to be a burden to examine both groups, and the restriction requirement **was withdrawn.**

Newly added claims 26-28 are dependent on the pending claims and appear consistent with the elected invention.

Claims 10-28 are pending and currently under examination as drawn to a method of analyzing a biological sample by comparing sequence reads obtained from a blood component and the comparison to samples taken at a different time from the first for patient screening are currently under examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/4/2022 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Priority

This application filed 10/5/2021 is a Divisional of 16/132123, now US Patent 11142802, which is a continuation of 14/929075, now US Patent 10125399, which claims benefit to US provisional application 62/072936 filed 10/30/2014; and is related to 17/065406 filed 10/7/2020 through parent 16/132123, and to PCT/US15/58483 filed 10/30/2015; and is the parent to US application 17/748200 filed 5/19/2022, which is the parent US application 17/828572 filed 5/31/2022.

No comment on the priority summary is provided by Applicants in the instant response.

Double Patenting

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).

Examiner note:

A terminal disclaimer filed 3/29/2022 was received and APPROVED over the claims of U.S. Patent No. 11142802 (16/132123 allowed 8/9/2021), U.S. Patent No. 10125399 (14/929075 allowed 10/24/2018), and over the claims of copending Application No. 17/065406 (RCE filed 1/28/2022). Upon search of inventors, newly filed applications have been identified.

Claims 10-28 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of copending Application No. 17/828572 filed 5/31/2022 (restriction mailed 7/25/2022). Although the claims at issue are not identical, they are not

patentably distinct from each other because each is drawn to a method for evaluating recurrence of a disease by steps that require evaluating/detecting variations over time from a tissue and providing the results in the form of a report. A copy of the pending claim 10 from '572 is provided for comparison.

10. (Previously presented) A method for detecting a presence or recurrence of a disease, comprising:

(a) obtaining at least a first tissue sample and a second tissue sample from a subject;

(b) extracting nucleic acid molecules from (i) the first tissue sample to obtain a first set of nucleic acid molecules, and (ii) the second tissue sample to obtain a second set of nucleic acid molecules;

(c) independently sequencing the first set of nucleic acid molecules and the second set of nucleic acid molecules to generate a first set of sequence reads and a second set of sequence reads;

(d) comparing with a programmed computer processor the first set of sequence reads and the second set of sequence reads to identify a first set of mosaic variants specific to the subject;

(e) generating in computer memory a relationship between the first set of mosaic variants specific to the subject, the first tissue sample, and the second tissue sample to provide a mutation map of the subject; and

(f) based on the mutation map, creating a report thereby detecting the presence or recurrence of the disease in the subject.

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

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-25 rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement **is withdrawn.**

Specifically, the limitation of excluding from the claim the active steps for use of a blood sample from a 'non-fetal source' has been deleted. It is noted that the pre-amble has been amended to recite a wherein clause that the biological sample is a non-fetal source, which appears generally supported by the teaching to evaluate two or more tissues from a patient, and the teaching to use leukocytes as a control source/reference of a patient's genome. More generally for the source to be one or more and any tissue, the specification teaches at [0197]:

"These ***samples are obtained from all over the individual's body*** *and can include samples from blood, a skin biopsy, a hair sample, and the like*. Nucleic acids are extracted from the samples and are sequenced by whole genome sequencing (WGS) to identify differential mutations between the various tissue samples. At some time in the future, the individual undergoes a procedure (e.g., a colonoscopy). A biopsy of the tissue (e.g., a biopsy of the colon) is taken during the procedure, nucleic acids are extracted from the biopsy, and the nucleic acids are sequenced to identify additional differential mutations. The differential mutations are mapped onto the developmental tree by associating the tissue source on the tree to the differential mutation. For example, a mutation is identified in the sample obtained from the pancreas, but not in lungs. This suggests that the mutation occurred sometime during branching of the primitive gut to the lungs and the digestive tube. All of the identified mutations are mapped in this fashion generating a comprehensive developmental mutation map."

Claims 10-39 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for applications subject to pre-AIA 35 U.S.C. 112, the inventor(s), at the time the application was filed, had

possession of the claimed invention. Specifically, the scope of the claim as provided in claim 11 of identifying 'second mosaic variants specific to said tissue sample of said subject in a second additional sample' where the 'sample is obtained from a source or at a time point that is different than said tissue sample and said first additional sample'. In review of the specification, while the guidance provides for the analysis of a variety of tissue sources, it does not appear to support analyzing a first tissue then a second different tissue to identify mosaic variants specific to the first tissue.

Amending the claims to provide that the additional sources/samples are from the same tissue, or that analysis of cfDNA is the basis of later time points could address the basis of the rejection.

> The following is a quotation of 35 U.S.C. 112(b):
> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
>
> The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-25 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention for the limitation of 'separated from a blood sample of said subject from a non-fetal source' **is withdrawn.**

The amendment to the claims to delete 'non-fetal source' has addressed the issue.

Claims 10-39 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention. Specifically, the claims have been amended from extracting two sources of nucleic acids from blood, to one that provides the first sample being a tissue and the second being leukocytes found in the blood, and at issue are subsequent steps for the source of the 'additional sample' that is 'different' (see step (c) as amended and claim 11 for example which appears to require another different source be used). It is unclear if 'different' is meant to modify 'time' or both time and sample source. Providing a different sample source appears generally supported by the specification for possible sources being analyzed, but not in the steps as specifically set forth and it is unclear how mosaic variations would be used or be informative if they are analyzed in a different tissue source than the one used in the initial steps establishing its presence. Dependent claims provide for a choice in the source of sample, but fail to provide a clear indication to how the initial steps and choices are intended to limit subsequent steps and analysis.

More clearly setting forth the nature of the sample, the specific extraction steps that differentiate the two sources that are used in subsequent steps, or limitations consistent with the specification for how sequences are obtained in step a) to differentiate the two sources would address the basis of the rejection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10-26 **stand** rejected **and newly added claims 26-28 are rejected** under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter because the claimed invention is not directed to patent eligible subject matter. Based upon an analysis with respect to the claim as a whole, claims 10-28 do not recite something significantly different than a judicial exception. The rationale for this determination is explained below.

Claim analysis

Independent claims 10 and 20 have been amended and still are directed generally towards a method of screening for cancer (versus any disease) by detecting variants from a tissue as compared to a reference of leukocytes present in the blood of a patient, and reporting possible observed changes over time. The claims have been amended to indicate that the first sample is a tissue (versus components/cfDNA from the blood), provide for additional specificity to the identification of subsequent samples, and that the final step provides for a report of any identification of a variant and that the variant is correlated to predicting, diagnosing, and/or prognosing a status or outcome of a cancer. The claim sets forth the steps of obtaining reads for two samples from a subject, one representing a tissue and one representing leukocytes, and subsequent steps provide additional samples from a tissue or blood, obtaining reads of the nucleic acids reads that are present in the samples by sequencing the nucleic acids that are present, and comparing the sequence data identifying possible variants that may be present between the two where the reads from the leukocytes is to be designated 'normal' in the analysis. Claim 20 has been amended, and still is directed to separating blood into cfDNA and leukocytes to obtain samples which are sequences and the reads produced are used in the analysis over time. Dependent claims set forth the types of variations that might be detected, such as copy number, SNPs, MNPs, inDels,.. or that the variant is associated with disease and/or possible treatment and

that the method steps can be performed more than once at different time points for comparison of the variants at different times.

For step 1 of the 101 analysis, claims 10-28 are found to be directed to a statutory category of a process. As amended the claims require obtaining reads by sequencing nucleic acid molecules obtained from the biological samples of the patient for comparison and analysis of differences in the read data between the two samples.

For step 2A of the 101 analysis, the judicial exception of the claims are the steps of accessing and analyzing sequence read data for differences/variants. The step of aligning and comparing sequence to arrive at the identification of variations between sequences are considered instructional steps. In view of the specification, the claim requires analyzing homology or computing similarity scores to determine differences in the sequences. The judicial exception is a set of instructions for analysis of sequence data, and appears to fall into the category of Mental Processes that is concepts performed in the human mind (including an observation, evaluation, judgment, opinion). Here, the claims do not require a computer, or any large amount or complexity of read sequence data, and could be performed on paper and the analysis could be performed in one's mind by comparing two sequences to see if there is any variant base between the two. Dependent claims recite comparison of other sources and that multiple variants might be detected, but similar to comparing two sequences it does not appear beyond observation to align and identify differences among sequences and call them variants. For the additional step of providing a report, in review of the specification this generically and broadly provides for reporting what differences were observed. Further, as the final step has been amended to recite '<u>wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in a subject</u>', this appears to be instruction and conditional on

what if anything is observed in comparing the sequence reads, and in view of the specification the ability to provide this would be derived from sources and teachings outside the specification which provides such correlations relative to variants associated with cancer.

Recent guidance from the office requires that the judicial exception be evaluated under a second prong to determine whether the judicial exception is practically applied. In the instant case, the claims require an additional element of 'obtaining' which requires a physical step to create the sequence read data by sequencing nucleic acids isolated from a sample. In review of the specification, the methods of sample preparation and nucleic acid isolation and sequencing are performed by methods known in the art. With respect to providing sources from blood that include separation of leukocytes and the remaining cfDNA, and further analysis and comparison of the two, Lo et al. (1997) provide specific method steps for separating and comparing the two nucleic acid sources present in a blood sample. With respect to the subsequent analysis and reporting, this judicial exception requires steps recited at high level of generality and is not found to be a practical application of the judicial exception as broadly set forth, and provides for known combination of steps used in obtaining sequence read data (see also present specification for generalized listing of possible methods that can be use in the context of the steps). When the steps are viewed as physical steps or additional elements, it appears that the steps of obtaining sequence data/information and subsequently analyzing read data are separate from one another, and do not integrate back into the steps comprising additional elements. The claims require providing a report 'wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in a subject' however this appears to be generically directed to reporting the observation of the possible differences/variants between the aligned sequences that were observed, and any correlation would be derived from know correlations present in the art.

In this analysis, it appears that the step of obtaining sequence information is not integrated with the judicial exception and only provides the instruction to report what is observed, nor do the claims provide a practical application of the broad steps used to obtain sequence reads as a consequence of the analysis (as provided in the fact pattern in *Vanda*) for what is done with the information in a report.

For Step 2B of the two step analysis, one is to determine whether any element or combination of elements, in the claim is sufficient to ensure that the claim as a whole amounts to significantly more than the judicial exception. In review of the evidence of record and given the breadth of the claims, there does not appear to be additional steps that are recited in the instantly claimed invention that would amount to significantly more than obtaining read data for analysis within the judicial exception. In this case the judicial exception is the information of where a given read aligns with a normal or reference sequence to potentially identify variations between reads. More specifically, it is noted that at the time of filing that using circulating cell free DNA was known and used for diagnostic methods and used for cancer intervention (see for example the teachings of Lo et al., De Mattos-Arruda et al. and Laktionov et al.) and are considered as known and conventional steps of obtaining and separating nucleic acids in a sample and obtaining genetic information about a patient. As such, the instant claims are drawn only to an abstract process that only manipulates genetic data and the judicial exception of a natural phenomenon (identification of variant sequences in circulating cell free DNA versus a tissue), and are not directed to statutory subject matter. Dependent claims that set forth the use of an array or bead to capture specific sequences or the use of amplification to provide greater copy number for sequence analysis for analysis in the judicial exception, do not appear to be novel and appear to be a conventional means for 'enriching' or 'capturing' a sequence of interest (claims

20-24) from a sample as a step of isolation or purification consistent with the disclosure of the present specification. Therefore the result of the analysis is that the claims are directed towards a judicial exception, i.e. an abstract idea. In the instant case, the claims are directed to only the analysis and manipulation of data.

Without additional limitations, a process that employs mathematical algorithms or general considerations to manipulate existing information (in this case defining the presence/absence of variants/alleles in a mixed sample) to generate additional information (in this case describing the nucleic acids present in a sample) is not patent eligible. Furthermore, if a claim is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is non-statutory. In other words, patenting abstract ideas cannot be circumvented by attempting to limit the use [the idea] to a particular technological environment. For the instant claims, it is noted that a computer and/or program/product can be used to compare sequence reads for homology or variation (specification provides guidance for available tools), but this amount to mere instruction to implement an abstract idea in a computer environment. The hardware contemplated in the specification for the analysis do not offer a meaningful limitation beyond generally linking "the use of the method to a particular technological environment,' that is, implementation via computers." see Alice Corp v. CLS Bank Int'l 573 U.S. (2014). For the reasons set forth above, the claims are not considered to recite something significantly different than a judicial exception and thereby are not directed to patent eligible subject matter.

Response to Applicant's arguments

For step 1, Applicants argue that the claims require 'sequencing' and are a statutory category.

In response, the basis of the rejection above acknowledges Applicants position, and the examiner agrees the claims as amended are directed to a statutory category.

For step 2A, Applicants note the guidance of the 2019 Guidance Update and argue that the rejection does not follow the two prong approach.

In response, it is noted that the 2019 Guidance Update is no longer in force, and reliance on the MPEP is the official guidance of the office. With respect evaluating the claims in a two prong approach in step 2A, the basis of the rejection clearly provides an indication of judicial exception, and provides explicitly that under prong two the judicial exception is analyzed for its practical application.

Applicants argue that none of the claims recite a judicial exception that is a mental process, and can not be practically performed in the human mind. Noting the guidance of the specification, Applicants argue that based on the possible size of a template and possible number of reads, a person can not realistically perform each of the operations for the claim for this amount of data.

In response, initially it is noted that the amount of read data produced is not a limitation or requirement of the claims. However, even if it were a large amount of sequence reads that had to be evaluated, the steps that are required to be performed of the claims, that is the process of comparing and aligning two sequences do not appear to be beyond the ability of observation and the human mind. Providing more sequences for comparison does not make the claim requirements for what is practiced any more difficult, it just would have to repeated more times.

Under prong 2, Applicants maintain that the claims are similar to McRO, and provide an improvement to the filed of cancer diagnostics because the method provides and improved

detection only requiring an initial tissue sample, and allows for downstream monitoring without invasive monitoring.

In response, respect to the judicial exception and analysis of the read data obtained, the fact pattern provided in *McRO* appears different from that of the instant claims. Here, the analysis steps are not integrated into a process like that of CGI in *McRO* that addressed a problem previously performed manually, but rather applies steps that simply analyze data that is obtained. It is noted that neither the specification nor the claims provides new means for comparing sequences or identifying variants as generically provided, and reporting as a final step broadly provides for indicating what the results were if any were identified. With respect to arguments that the claims only require one tissue sample, this appears in opposition to the claim requirments of step c) which requires subsequent additional samples over time from a tissue. While one can provide blood in subsequent steps to monitor the cfDNA it contains, the art clearly the art of record demonstrates that methods of isolating cfDNA from leukocytes was known and practiced, and that variations in the reads between the two could be observed, and does not appear to provide an improvement. Again, the methods of obtaining nucleic acids, sequencing to provide reads and the comparison of reads are all performed by means known in the art, and the claims and the evidence of record do not appear to provide any improvement in detection or the field of cancer diagnostics in general.

For step 2B, Applicant argue that the claims provide steps that are not well known or conventional, and qualify as significantly more. Applicants argue that the steps of the claims are not provided in any of the cited references and viewed as a whole are more than steps of isolating DNA from blood components and providing correlations of disease based on the comparison of read data.

In response, Lo et al was cited to demonstrate that separation of cfDNA and the use of leukocytes as a reference was known. While not provided in the basis of the 101, the references cited in the art rejection provide further evidence that cancer could be monitored over time, and changes could be detected and evidence the idea of monitoring over time in the care of a cancer patient. The analysis for the combination of additional elements here relies on the physical steps of isolating and sequencing nucleic acids from two samples which Lo et al provides, and does not appear to provide significantly more. Moreover, the analysis is comparison of the read data for possible differences that might exist, and in review of the specification there are no new or unobvious means to compare the sequences nor new correlations derived from the method steps practiced as a whole, and do not appear to improve cancer monitoring in a patient.\ as applicant arugues.

Applicants arguments and claim amendments have been fully considered, but not found persuasive. In summary aas provided above, the steps considered additional elements for isolating and sequencing DNA from a blood sample have been acknowledged, and Lo et al has been cited and discussed that this step was known and practiced in the prior art, and for the same purpose of comparing cfDNA to leukocytes as a control. Further, the specification provides no new correlations of disease based on obtaining read data, and it was readily known that certain genetic alterations were known to be associated with the progression of cancer, as well as alterations associated with other conditions and diseases all of which the present claims and disclosure rely upon to practice the claims as broadly set forth. Unlike the fact pattern in *McRO* which provided an automated set of rules that addressed a problem previously resolved manually, the present claims broadly provide for known steps of isolating two known sources of DNA in blood, and using leukocytes as a control which was also taught (by Lo et al). Given the

evidence of record and breadth of the claims, Applicant's arguments that the steps provide an improvement and significantly more do not appear to be consistent with the fact pattern and evidence of record that the claims are patent eligible as provided in *McRO*. Further, given the evidence of record, the art provides that read data could be observed and could be correlative to diseases such as cancer. Therefore, for the reasons above and of record, the rejection **is maintained**.

As noted previously, one way to overcome a rejection for non-patent-eligible subject matter is to persuasively argue that the claimed subject matter is not directed to a judicial exception. Another way for the applicants to overcome the rejection is to persuasively argue that the claims contain elements in addition to the judicial exception that either individually or as an ordered combination are not well understood, routine, or conventional. Another way for the applicants to overcome the rejection is to persuasively argue that the claims as a whole result in an improvement to a technology. Persuasive evidence for an improvement to a technology could be a comparison of results of the claimed subject matter with results of the prior art, or arguments based on scientific reasoning that the claimed subject matter inherently results an improvement over the prior art. The applicants should show why the claims require the improvement in all embodiments.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 10-25 as amended **stand** rejected and **newly added claims 26-28 are** rejected under 35 U.S.C. 103 as being unpatentable over Lo et al. (1997), Benesova et al. (2013), De Mattos-Arruda et al. (2013), Laktionov et al. (2004), Ellinger et al (Urologic Oncology 29:124-129 (2001)), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)), Shaw et al (Genome Research 22:220-231 (2012)), Lewis et al. (US 2012/0058480 A1) and Green et al. (US 2005/0260645 A1).

Independent claims 10 and 20 have been amended and still are directed generally towards a method of screening for cancer (versus any disease) by detecting variants from a tissue as compared to a reference of leukocytes present in the blood of a patient, and reporting possible observed changes over time. Claim 20 has been amended, and still is directed to separating

blood into cfDNA and leukocytes to obtain samples which are sequenced and the reads produced are used in the analysis over time, and does not require a tissue as a source. Claim 10 has been amended to indicate that the first sample is a tissue (versus components/cfDNA from the blood as present in claim 20), provide for additional specificity to the identification of subsequent samples, and that the final step provides for a report of any identification of a variant and that the variant is correlated to predicting, diagnosing, and/or prognosing a status or outcome of a cancer. Both sets provide for analyzing two different samples where leukocytes are a control, and determining if variants in the reads exist which might be indicative or associated with cancer monitoring in a patient. The claim sets forth the steps of obtaining reads for two samples from a subject, one representing a tissue and one representing leukocytes, and subsequent steps provide additional samples from a tissue or blood, obtaining reads of the nucleic acids reads that are present in the samples by sequencing the nucleic acids that are present, and comparing the sequence data identifying possible variants that may be present between the two where the reads from the leukocytes is to be designated 'normal' in the analysis. Dependent claims set forth the types of variations that might be detected, such as copy number, SNPs, MNPs, inDels,.. or that the variant is associated with disease and/or possible treatment and that the method steps can be performed more than once at different time points for comparison of the variants at different times.

Benesova et al. teach mutation-based detection and monitoring of cell-free tumor DNA in peripheral blood of cancer patients. More specifically, Benesova et al provide recent development in methodologies allows screening for a presence of cell-free DNA as a new viable tool in early detection and management of major cancers. In the methods taught, Benesova et al provide the step to distinguish tumor cfDNA from nontumorous cfDNA, specific somatic DNA

mutations, previously localized in the primary tumor tissue, are identified in the extracted cfDNA, and provide the basis of comparing tumor tissue with controls and subsequent analysis of cfDNA for monitoring. Lo et al provide a report for the presence of cfDNA in maternal plasma and serum, and note that the presence of tumor DNA has been found and analyzed in cancer patients. The methods disclosed by Lo et al. used a rapid-boiling method to extract DNA from plasma and serum. DNA from plasma, serum, and nucleated blood cells from 43 pregnant women underwent a sensitive Y-PCR assay to detect circulating male fetal DNA from women bearing male fetuses. More specifically, maternal human blood samples were processed 1–3 h after venesection. Blood samples were centrifuged at 3000 *g*, and plasma and serum were carefully removed from the nucleic-acid-containing and plain tubes, respectively, and transferred into plain polypropylene tubes. Great care was taken to ensure that the buffy coat or the blood clot was undisturbed when plasma or serum samples, respectively, were removed. After removal of the plasma samples, the red-cell pellet and buffy coat were saved for DNA extraction with a Nucleon DNA extraction kit. The plasma and serum samples then underwent a second centrifugation at 3000 *g*, and the re-centrifuged plasma and serum samples were collected into fresh polypropylene tubes. Similar to Lo et al suggestion, Mattos-Arruda et al. provide for the teaching that circulating blood biomarkers promise to become non-invasive real-time surrogates for tumour tissue based biomarkers. Circulating biomarkers have been investigated as tools for breast cancer diagnosis, the dissection of breast cancer biology and its genetic and clinical heterogeneity, prognostication, prediction and monitoring of therapeutic response and resistance. Laktionov et al. provide further evidence and teaching that both DNA and RNA can be identified and analyzed for method to diagnose cancer. Laktionov et al. provide that in the blood there are

two sources, a free from and one that is bound to blood cells, such as leukocytes which possess nucleic acid binding proteins at their surface.

In addition, Lo et al provide that future studies should investigate the temporal relation between gestation and the appearance and concentration of fetal DNA in maternal plasma. As well as sex-linked disorders, techniques for fetal-DNA detection in maternal plasma or serum can also be used to detect many paternally inherited DNA sequences that differ from their maternal counterparts. Clinical examples include fetal rhesus D status assessment and detection of certain haemoglobinopathies. The plasma or serum-based approach might also be applicable to screening for chromosomal aneuploidies (such as Down's syndrome) if there is a quantitative difference in the concentration of fetal DNA in maternal plasma and serum between affected and normal pregnancies; this is a situation analogous to the high concentration of fetal cells detectable in pregnancies that involve aneuploid fetuses. Laktionov et al provide the observation for different stages of cancer providing different amounts of nucleic acids being bound when analyzing different patients and different stage samples. Further, it is noted by Lo et al. and acknowledged that there are interesting similarities between a growing fetus and a neoplasm: both are immunologically foreign and have an extensive vascular interface with their hosts, noting the results as analogous to that of Nawroz and colleagues, who detected in head and neck cancer patients mutant plasma DNA predominantly in those with high tumor load. Similar to Nawroz noted by Lo et al. at the time of filing, the presence of circulating cell-free DNA in humans was known as evidenced by Ellinger et al, Jung et al and Shaw et al. who provide detailed examples of how cell-free circulation DNA can be used to evaluate patients with cancer. Each Ellinger et al, Jung et al and Shaw et al. provide a detailed analysis to provide evidence that isolated cell free DNA can be used to identify genetic variants in cancer patients, both in quantity

and in specific mutations associated with a given cancer and possible roles for treatment or care. Similar to Lo et al., Lewis discloses methods for separating cell-free DNA from a maternal blood sample (para [0010] "The present invention provides methods for enriching fetal nucleic acids from a maternal sample, such as, whole blood .... obtained from a pregnant female") and that analysis of fetal cell-free DNA offers one potential approach to non-invasive prenatal diagnosis" (para [0005] "Analysis of cell free fetal DNA (cffDNA) in maternal plasma offers one potential approach to non-invasive prenatal diagnosis"). Lewis further teaches that maternal cell-free DNA is also present in blood (para [0006] "cell free maternal DNA is also present in blood in quantitative excess"). Given that leukocytes are present in the buffy coat and serve as nucleated blood cells as provided in Lo et al. that can serve as a source of patient nucleic acid in a blood sample, one of ordinary skill in the art would have readily appreciated that nucleic acid extracted from maternal leukocytes can be compared to isolated cell free DNA in order to determine whether the cell free DNA is maternal or fetal cell free DNA, wherein fetal cell free DNA can be used to make a prenatal diagnosis of the growing fetus. Thus, one of ordinary skill in the art would have found it obvious to use the method of Lo et al to include a step of separating a maternal blood sample into at least a first component that includes cell-free nucleic acid molecules and a second component that includes a cellular fraction comprising leukocytes which are known to be present in the buffy coat, as taught by both Lo et al and Lewis, in order to verify that cell-free nucleic acid is from the fetus, and to use the fetal cell-free nucleic acid to provide a non-invasive prenatal diagnosis of the fetus, as taught by Lo et al and Lewis. Finally, in view of the art as a whole, the use of genetic markers can be used to detect whether cancer exists within the patient as well as determine the origin of the cancer based on the specificity of the genetic marker being used. The skilled artisan would know that specific types of identified cancers

would require different and unique types of treatments making obvious 'compositions' that would be used in the treatment of cancer.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Response to Applicant's arguments and claim amendments

Applicants note the amendment to the claims providing steps for clarification and argue that none of the references provide fail to provide early disease diagnosis reporting, where the early reporting is based on detection of a variant when comparing cfDNA sequences to that of leukocytes used as a control reference sequence obtained from the subject. The claim amendments and Applicants arguments have been fully considered, but not found persuasive.

To the extent that arguments apply to the instant claims, with respect to the amendment for an additional step of d) for providing a report, a review of the specification suggests that there is no new means for reporting, and that broadly this step and limitation provides for reporting what was observed as a form of data. Clearly, Benesova et al provide recent development in methodologies allows screening for a presence of cell-free DNA as a new viable tool in early detection and management of cancer in patients. As an initial step, Benesova et al provide the step to distinguish tumor cfDNA from nontumorous cfDNA that may be present by analyzing for specific somatic DNA mutations, previously localized in the primary tumor tissue, to later monitor the extracted cfDNA in the patient, and provide the basis of comparing tumor tissue with controls and subsequent analysis of cfDNA for monitoring. Given the teachings of Mattos-Arruda et al. and Laktionov et al. for the presence and correlation of markers that could be detected, it appears obvious that known correlations could be used and applied to reporting based on the information that results from the analysis of the read data of cfDNA versus a control.

A review of the arguments and evidence of record does not appear to provide for new methods of isolation or for reporting observations, or secondary considerations that comparing cfDNA to a control from a subject provides any unique result or requirement for analysis beyond aligning and comparing read data to observe potential differences. Further, it would have been expected that biomarkers correlated with a variety of conditions could be observed given the teachings of Mattos-Arruda et al. and Laktionov et al.

Therefore, for the reasons above and of record, the rejection **is maintained**.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph T Woitach whose telephone number is (571)272-0739. The examiner can normally be reached Mon-Fri; 9:00-5:00.

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, Karlheinz R Skowronek can be reached on 571 272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available

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/Joseph Woitach/
Primary Examiner, Art Unit 1631

Notice of References Cited	Application/Control No. 17/494,513	Applicant(s)/Patent Under Reexamination West, John	
	Examiner Joseph T Woitach	Art Unit 1631	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Benesova et al. Mutation-based detection and monitoring of cell-free tumor DNA in peripheral blood of cancer patients, Analytical Biochemistry Volume 433, Issue 2, 15 February 2013, Pages 227-234
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	Art Unit
	Joseph T Woitach	1631

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.

Foresight Ex1198 p. 209
Foresight v Personalis
IPR2024-00170

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	**Art Unit**
	Joseph T Woitach	1631

Search Notes		
Search Notes	**Date**	**Examiner**
reviewed applications/patents in priority listing	02/17/2022	jw
PALM for inventor and assignee/applicant	02/17/2022	jw
Google	02/17/2022	jw
SEARCH	02/17/2022	jw
Google	04/04/2022	jw
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Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

Foresight Ex1198 p. 210
Foresight v Personalis
IPR2024-00170

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1631
				Examiner Name	Joseph T. Woitach
Sheet	1	of	1	Attorney Docket Number	48929.4008/US03

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent Document Number	U.S. Patent Document Kind Code[1]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear

FOREIGN PATENT DOCUMENTS

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OFFICE ACTIONS/SEARCH REPORTS

Examiner Initials'	Cite No.	Country	Description (*for example,* Office Action (Examiner: J. Doe))	Date of Issuance MM-DD-YYYY	T[6]
	1	EP	Extended European Search Report for European Patent Application No. EP22153028.0, 10 pages.	06-09-2022	

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials'	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]

Examiner Signature	/Joseph Woitach/	Date Considered	08/17/2022

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicants unique citation designation number (optional). [2]See Kinds of U.S. Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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 govern by 35 USC 122 and 37 CFR 1.14. This collection is estimated to take 2 hours 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 are required 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, Mail Stop Amendment, P.O. Box 1450, Alexandria, VA 22313-1450

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 08/12/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
08/12/2022	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
jmichel@orrick.com
vsantos@orrick.com

Foresight EX1108-p. 214
Foresight v Personalis
IPR2024-00170

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 17/494,513	**Applicant(s)** West, John	
	Examiner JoAnne L Burke	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 04 August 2022 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 JoAnne Burke at (571)272-4584. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/JOANNE L BURKE/ Lead Paralegal Specialist, OPET	

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	17494513	Filing Date	2021-10-05	Docket Number (if applicable)	48929.4008/US03	Art Unit	1631
First Named Inventor	John West			Examiner Name	Joseph T. Woitach		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☒ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☒ Other CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e)

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.
☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 150665

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

X Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Alex Straughn/	Date (YYYY-MM-DD)	2022-08-04
Name	Alex Straughn	Registration Number	80155

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor: **John WEST**	Examiner: **Joseph T. Woitach**
U.S. Serial No.: **17/494,513**	Art Unit: **1631**
Filing Date: **October 5, 2021**	Confirmation No.: **8186**
For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Attorney Docket: **48929.4008/US03**

Patent Center
Commissioner for Patents

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Sir:

In accordance with 37 CFR §§ 1.97 and 1.98, the items identified in this Information Disclosure Statement ("IDS") are brought to the attention of the Office. The items are listed on the attached form PTO/SB/08a (PTO-1449). In accordance with the USPTO waiver of the requirement under 37 CFR § 1.98(a)(2)(i), only copies of foreign patent documents and non-patent literature are enclosed for the convenience of the Examiner.

The items identified in this IDS may or may not be "material" pursuant to 37 CFR § 1.56. The submission thereof by Applicant is not to be construed as an admission that any such patent, publication or other information referred to therein is material or considered to be material (37 CFR § 1.97(h)), or even qualifies as "prior art" under 35 USC § 102 with respect to this invention unless specifically designated by Applicant as such.

INFORMATION DISCLOSURE STATEMENT FILING PROVISION:

☒ This IDS is believed to be timely in that it is being submitted under 37 CFR § 1.97(b), that is (1) within three months of the filing date of the application, which is not a continued prosecution application filed under § 1.53(d); or (2) within three months of entry of the national stage as set forth in 37 CFR § 1.491; or (3) before the mailing of a first Office Action on the

merits; or (4) before the mailing of a first Office Action after filing a request for continued examination under § 1.114. Thus, no fee is required.

☐ However, if the undersigned is in error in this regard, Applicant respectfully requests that the Office consider this IDS as filed under 37 CFR § 1.97(c), if applicable, and charge the fee due under 37 CFR §1.17(p) to the deposit account referenced below.

☒ However, if the undersigned is in error in this regard, Applicant respectfully requests that the Office consider this IDS as filed under 37 CFR § 1.97(c), if applicable, and a statement under 37 CFR § 1.97(e) is included below, thus no fee is required.

☐ This IDS is being submitted under 37 CFR § 1.97(c), that is after mailing of a first Office Action on the merits, but before a Final Action under 37 CFR § 1.113 or a Notice of Allowance under 37 CFR § 1.311.

☐ The fee due under 37 CFR § 1.17(p) is submitted herewith.

☐ A statement under 37 CFR § 1.97(e) is included below, thus no fee is required. In the event that this IDS is not received before a Final Action or a Notice of Allowance, then Applicant respectfully requests that the Office consider the filing of these papers to be submitted under 37 CFR § 1.97(d) and charge the fee due under 37 CFR § 1.17(p) to the deposit account below.

☐ This IDS is being submitted under 37 CFR § 1.97(d), that is after a Final Action under 37 CFR § 1.113 or a Notice of Allowance under 37 CFR § 1.311, but before payment of the issue fee. A statement under 37 CFR § 1.97(e) is included below. The fee due under 37 CFR § 1.17(p) is submitted herewith ($260.00 – large entity).

☐ This IDS is being submitted after a payment of the issue fee. A statement under 37 CFR § 1.97(e) is included below. The Certification and Request for Reconsideration of an IDS filed after payment of the issue fee under QPDIS Pilot Program is included. The EFS-Web e-petition is included. The fee due under 37 CFR § 1.17(p) is submitted herewith ($260.00 – large entity).

STATEMENT UNDER 37 CFR § 1.97(e):

☒ Each item contained in this IDS 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 this IDS.

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

STATEMENT UNDER 37 CFR § 1.98(d)(1):

☐ Copies of patents, publications, pending US applications or other information, as specified in 37 CFR § 1.98(a), listed on the Information Disclosure Statement are NOT required. The subject application is a continuation, divisional, or continuation-in-part, and relies on the earlier application for an effective filing date under 35 USC § 120.

STATEMENT UNDER 37 CFR § 1.704(d):

☐ Each item contained in this IDS was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

☐ Each item contained in this IDS was a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

PAYMENT AND/OR AUTHORIZATION TO CHARGE FEES:

☐ A check in the amount of _____ is enclosed for the above fee(s).

☐ Please charge _____ to Deposit Account No. **15-0665** for the above fee(s).

☒ The Commissioner is authorized to charge any fees required by the filing of these papers, and to credit any overpayment to Orrick, Herrington & Sutcliffe's Deposit Account No. **15-0665**.

Respectfully submitted,

ORRICK, HERRINGTON & SUTCLIFFE LLP

Dated: 8-4-2022

By: /Alex Straughn/
Alex Straughn, Reg. No. 80,155
for Gargi Talukder, Reg. No. 61,368

ORRICK, HERRINGTON & SUTCLIFFE LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
949/567-6700 Telephone 949/567-6710 Facsimile

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
17/494,513	08/04/2022 03:00:38 PM ET	48929.4008/US03

Title of Invention

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	8186	FILED BY	Sheila Gloss
PATENT CENTER #	60842904	AUTHORIZED BY	Alex Straughn
CUSTOMER #	182685	FILING DATE	10/05/2021
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	John West

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 150665	E202284F01032851	Sheila Gloss

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2817	REQUEST FOR PRIORITIZED EXAMINATION	2100.00	1	2100.00
2251	EXTENSION FOR RESPONSE WITHIN FIRST MONTH	110.00	1	110.00
2830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	70.00	1	70.00
2801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	680.00	1	680.00
			TOTAL AMOUNT:	$2,960.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized

by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
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CUSTOMER #	182685	FIRST NAMED INVENTOR	John West
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Alex Straughn

Documents

TOTAL DOCUMENTS: 9

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
48929.4008_US03_FOAResponse.pdf		23	-	217 KB
48929.4008_US03_FOAResponse-A.NE.pdf	(1-1)	1	Response After Final Action	110 KB
48929.4008_US03_FOAResponse-CLM.pdf	(2-6)	5	Claims	122 KB
48929.4008_US03_FOAResponse-REM.pdf	(7-23)	17	Applicant Arguments/Remarks Made in an Amendment	206 KB
48929_4008US03_EOT.pdf		2	Extension of Time	160 KB

48929_4008US03_RCE.pdf	3	Request for Continued Examination (RCE)	1644 KB
48929_4008US03_TRK1Req.pdf	2	Track One Request	109 KB
48929_4008US03_SIDSTransmittal.pdf	4	Transmittal Letter	132 KB
48929_4008US03_SIDSForm.pdf	1	Information Disclosure Statement (IDS) Form (SB08)	163 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
EESR.pdf	10	Other reference-Patent/Application/Search Documents	336 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
48929.4008_US03_FOAResponse.pdf	9A7E9CB4DF7E507E17CFDD4E15B689499AA0158362855076E63C69C3A4D69477AA2920C859743FF1904F059DB045AA039C083AB5C96B9D1F8BEC09A2947E5E49
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48929.4008_US03_FOAResponse-REM.pdf	ACF0AD72F10B909AEDA9FC5024FBC68782D8C0987E359C2EDA09821FCB530D3005E6700E0B1FB06D3A37E3DFBF6A0139809649A6A8B5F730D76038149B432B93

48929_4008US03_EOT.pdf	150666AB848185142A28678495CEE0718E64C31854941A04A3D06B37D149B7BCB67541A2462E57CFD54CF2D42FE7298D2EB985717CBB1F5A952FA37B052CCA4D
48929_4008US03_RCE.pdf	85ED8CE851C0BE0880B958E307A7AE3892CF2819882848766F2352C06756EFD5067FEFCEB183446FFE045DA12A16DF69F433B8100AE5046DE7B295F3489B4301
48929_4008US03_TRK1Req.pdf	F09A593821C478220A70897CF511B8A69EBB7CAD65599891F3C9DE304B7368924281F0FC3AD2D735CF36FF07883D31CB4513D9AAAB06ACFEEA44355BC656D275
48929_4008US03_SIDSTransmittal.pdf	7B25030F29E00B70166F2E677C1F4DFFC8D97778C3B54115C01623B054485F43033E60EB5702F76D2D4039881668D8B946C26A712518958E43FF018A3AC33D6B
48929_4008US03_SIDSForm.pdf	C916EB6B3950D9F8137A10532567D3498CCB00C0AEDF7270B85A0E0CCC5708CA520422A7B870E88E9F177CDC920D3EE0539246EB75835E6CE73134874920AA7E
EESR.pdf	F76C605D22F77CFFA7C7A842178557E21188CDCDFF3BD41F862E45C85C7027F3E2AD9A87CE6BE907C8D6030EF5C7FA3392E7288E87A65232D82A4F1C26482234

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

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New International Application Filed with the USPTO as a Receiving Office

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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:	John West	Nonprovisional Application Number (if known):	17/494,513
Title of Invention:	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN		

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 /Alex Straughn/	Date 8-4-2022
Name (Print/Typed) Alex Straughn	Practitioner Registration Number 80,155

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 _____ 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/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): 48929.4008/US03

Application Number: 17/494,513

Filed: October 5, 2021

For: METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Art Unit: 1631

Examiner: Joseph T Woitach

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

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

	Fee	Small Entity Fee	Micro Entity Fee	
☑ One month (37 CFR 1.17(a)(1))	$220	$110	$55	$ 110
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$
☐ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$
☐ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$

☑ Applicant asserts small entity status. See 37 CFR 1.27.

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

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

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

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 150665.

☑ Payment made via EFS-Web.

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

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 80,155.

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

/Alex Straughn/ — Signature

8-4-2022 — Date

Alex Straughn — Typed or printed name

713-658-6427 — Telephone Number

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (use as many sheets as necessary)				Complete if Known	
				Application Number	17/494,513
				Filing Date	October 5, 2021
				Applicant	Personalis, Inc.
				Art Unit	1631
				Examiner Name	Joseph T. Woitach
Sheet	1	of	1	Attorney Docket Number	48929.4008/US03

U.S. PATENT DOCUMENTS

Examiner Initials	Cite No.	U.S. Patent Document Number	U.S. Patent Document Kind Code[1]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No.	Foreign Patent Document Office[2]	Foreign Patent Document Number[3]	Foreign Patent Document Kind Code[4]	Name of Patentee or Applicant of Cited Document	Date of Publications of Cited Documents MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Figures Appear	T[6]

OFFICE ACTIONS/SEARCH REPORTS

Examiner Initials'	Cite No.	Country	Description (*for example,* Office Action (Examiner: J. Doe))	Date of Issuance MM-DD-YYYY	T[6]
	1	EP	Extended European Search Report for European Patent Application No. EP22153028.0, 10 pages.	06-09-2022	

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS

Examiner Initials'	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicants unique citation designation number (optional). [2]See Kinds of U.S. Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1631
PERSONALIS, INC.	Examiner: Joseph T. Woitach
Serial No.: 17/494,513	Customer No. 182685
Filed: October 5, 2021	Confirmation No. 8186
For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Attorney Docket No. 48929.4008/US03

Filed via Patent Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO FINAL OFFICE ACTION

Commissioner:

This communication is responsive to the Final Office Action of April 11, 2022. This response is being filed on or by August 11, 2022, along with an appropriate extension of time, making it a timely filed response. A Request for Continued Examination (Form PTO/SB/30EFS) and required fees are submitted herewith. A Certification and Request for Prioritized Examination (Form PTO/AIA/424) and required fees are also submitted herewith.

Amendments to the Claims begins on page 2 of this paper; and

Remarks begin on page 7 of this paper.

Certificate of EFS-Web Transmission

Date: August 4, 2022

I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO.

/Sheila Gloss /
SHEILA GLOSS
4137-1838-5208.8

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listing of claims in the application.

1-9. (Canceled)

10. (Currently amended) A method of analyzing a biological sample obtained from a subject being screened for a ~~disease~~ cancer, wherein the biological sample is from a non-fetal source, the method comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by ~~independently~~ sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, and wherein (i) said first set of nucleic acid molecules is extracted from ~~a first component separated from a blood~~ tissue sample of said subject ~~from a non-fetal source~~, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a ~~second component separated from said~~ blood sample ~~from a non-fetal source~~;

(b) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(c) subsequent to (b), identifying said one or more ~~second~~ first mosaic variants specific to said tissue sample of said subject in a ~~second~~ first additional sample of said subject, wherein said ~~second~~ first additional sample is obtained from a source ~~or~~ and at a time point that is different than said ~~blood~~ tissue sample; and

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(d) providing a report based on an identification of said one or more first mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said subject ~~or said second mosaic variants~~.

11. (Currently amended) The method of claim 10, further comprising identifying one or more ~~third~~ second mosaic variants specific to said tissue sample of said subject in a ~~third~~ second additional sample of said subject, which ~~third~~ second additional sample is obtained from a source or at a time point that is different than said ~~blood~~ tissue sample and said ~~second~~ first additional sample.

12. (Currently amended) The method of claim 10, further comprising providing a recommendation for a therapeutic intervention based on an identification of said one or more first mosaic variants specific to said tissue sample of said subject ~~or said second mosaic variants~~.

13. (Currently amended) The method of claim 10, wherein said ~~first component separated from said blood~~ tissue sample comprises ~~cell-free or surface-bound nucleic acid molecules~~ a metastatic tissue sample, a mixed tissue sample, a biopsy, or a core needle biopsy.

14. (Currently amended) The method of claim 11, wherein said first and/or second ~~or third~~ additional sample comprises a blood sample, ~~a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy,~~ a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample~~,~~ ~~or a breast milk sample~~ of said subject.

15. (Currently amended) The method of claim 11, wherein said one or more first[[,]] and/or second~~, or third~~ mosaic variants specific to said tissue sample of said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

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16. (Currently amended) The method of claim 11, wherein said one or more first[[,]] and/or second~~, or third~~ mosaic variants specific to said tissue sample of said subject are causal or predisposing for a ~~disease~~ cancer.

17. (Currently amended) The method of claim 11, wherein said one or more first[[,]] and/or second~~, or third~~ mosaic variants specific to said tissue sample of said subject are non-causal for a ~~disease~~ cancer.

18. (Currently amended) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, ~~second~~ first additional sample, or ~~third~~ second additional sample.

19. (Currently amended) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said tissue sample, blood sample, ~~second~~ first additional sample, or ~~third~~ second additional sample.

20. (Currently amended) A method for early disease detection in a subject using at least two samples from the subject, wherein the at least two samples are from a non-fetal source, said method comprising:

(a) obtaining a blood sample from said subject;

(b) extracting (i) a first set of nucleic acid molecules from a first component separated from a blood sample of said subject ~~from a non-fetal source~~ and (ii) a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample ~~from a non-fetal source~~;

(c) quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules present in said first component separated from a blood sample;

(d) comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity;

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(e) if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads generated by ~~independently~~ sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules;

(f) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said subject in said first set of sequence reads that is not present in said second set of sequence reads;

(g) subsequent to (f), identifying said one or more ~~second~~ first mosaic variants specific to said subject in a second sample of said subject, which second sample is obtained from a source or at a time point that is different than said blood sample; and

(h) providing a report based on an identification of said one or more first mosaic variants specific to said subject in said second sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in said subject ~~or said second mosaic variants~~.

21. (Previously presented) The method of claim 20, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

22. (Currently amended) The method of claim 20, further comprising identifying one or more ~~third~~ second mosaic variants specific to said subject in a third sample of said subject, which third sample is obtained from a source or at a time point that is different than said blood sample and said second sample.

23. (Currently amended) The method of claim [[20]] 22, wherein said second or third sample comprises a blood sample, a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy, a saliva sample, a buccal swab, a urine sample, a semen sample, or a cerebrospinal fluid sample ~~or a breast milk sample~~ of said subject.

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24. (Currently amended) The method of claim 20, further comprising providing a recommendation for a therapeutic intervention based on an identification of said one or more first mosaic variants specific to said subject ~~or said second mosaic variants~~.

25. (Currently amended) The method of claim [[20]] 22 wherein said one or more first[[,]] and/or second~~, or third~~ mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

26. (New) The method of claim 10, wherein said one or more first mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

27. (New) The method of claim 20, wherein said one or more first mosaic variants specific to said subject are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

28. (New) The method of claim 10, wherein said predicting, diagnosing, and/or prognosing of (d) comprises one or more of the following: (i) diagnosing a cancer, (ii) identifying a cancer, (iii) determining a stage of a cancer, (iv) assessing risk of a cancer, (v) assessing risk of cancer recurrence, (vi) assessing reproductive risk, (vii) assessing efficacy of a drug, (viii) assessing risk of an adverse drug reaction, (ix) predicting optimal drug dosage, (x) predicting drug resistance, or any combination thereof.

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REMARKS

A. Status of the claims

With this amendment, claims 10-20, and 22-25 have been amended, and new claims 26-28 are added. These amendments are fully supported throughout the specification, including at, for example, paragraphs [0046], [0068], [0074], [0132], [0133], and [0143]. Support for new claims 26-28 can be found at least in paragraphs [0068], [0117], and [0132] of the specification. Accordingly, claims 10-28 are currently pending in this application. Applicant respectfully requests entry of the claims as amended.

B. Rejection under 35 U.S.C. § 112(a)

The Office has rejected claims 11-25 under 35 U.S.C. §112(a) as allegedly failing to comply with the written description requirement. Applicant respectfully disagrees. In the office action dated April 11, 2022, the Office alleges that, "…the newly added limitation of excluding a blood sample from a non-fetal source is considered a new limitation not specifically contemplated in the present disclosure" (Office Action dated 4-11-2022, page 5).

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended independent claim 10 and independent claim 20 to clarify the "non-fetal source" element previously incorporated in the response to the non-final office action dated February 28, 2022. In the office action dated April 11, 2022, the Office alleges that, "…the specification **does** appear to **provide for a source that the subject is not a fetus**, however it does not appear to exclude that the sample itself not contain a fetal source of cfDNA…" (Office Action dated 4-11-2022, page 7 (emphasis added)). The independent claims have been amended to clarify that the biological sample of claim 10 and the at least two biological samples of claim 20 are from a subject that is not a fetus, as opposed to a sample itself that does not contain a fetal source of cfDNA.

Further, the Office alleges that, "[d]ependent claims are included in the basis of the rejection because they fail to clarify or address the issue." (Office Action dated 4-11-2022, page 7). Claims 11-19 depend from and include all of the elements of claim 10 and recited additional elements of particular advantage and utility, therefore the clarification to independent claim 10

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also applies to dependent claims 11-19. Claims 21-25 depend from and include all of the elements of claim 20 and recite additional elements of particular advantage and utility, therefore the clarification to independent claim 20 also applies to dependent claims 21-25.

In view of the foregoing, Applicant respectfully submits that claims 10-25 are in compliance with 35 U.S.C. §112(a). As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112(a) be withdrawn.

C. Rejection under 35 U.S.C. § 112(b)

The Office has rejected claims 10-25 under 35 U.S.C. §112(b) as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor regards as the invention. Applicant respectfully disagrees. In the office action dated April 11, 2022, the Office alleges that, "…it is unclear if the subject to be excluded should not be a fetus, or that the blood sample not contain fetal material and that the fetal source not exist or is somehow separated from other sources that may be present in the blood sample that is obtained." (Office Action dated 4-11-2022, page 8).

As noted above in the response to the 112(a) rejection, Applicant has amended independent claims 10 and 20 to clarify the "non-fetal source" element previously incorporated in the response to the non-final office action dated February 28, 2022. The independent claims have been amended to clarify that the biological sample of claim 10 and the at least two biological samples of claim 20 are from a subject that is not a fetus, as opposed to a sample itself that does not contain a fetal source of cfDNA. Claims 11-19 depend from and include all of the elements of claim 10 and recited additional elements of particular advantage and utility, therefore the clarification to independent claim 10 also applies to dependent claims 11-19. Claims 21-25 depend from and include all of the elements of claim 20 and recite additional elements of particular advantage and utility, therefore the clarification to independent claim 20 also applies to dependent claims 21-25.

In view of the foregoing, Applicant respectfully submits that claims 10-25 are in compliance with 35 U.S.C. §112(b). As such, Applicant respectfully requests that the rejections under 35 U.S.C. §112(b) be withdrawn.

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D. Rejection under 35 U.S.C. § 101

The Office maintains its rejection of claims 10-23 and rejects newly added claims 24-25 under 35 U.S.C. §101, because the claimed invention is allegedly directed to a judicial exception without significantly more. Applicant respectfully disagrees.

Applicant provides below a step-by-step rebuttal against the Office's assertion that the claims are not subject matter eligible under 35 U.S.C. §101. For the sake of clarity, Applicant initially provides a summary of the arguments set forth by the Office and then sets forth a summary of arguments in response to the Office's arguments. Citations can be found below in the point-by-point response to the arguments provided by the Office. In the office action dated April 11, 2022, the Office asserts that: (1) claims 10-19 are not directed to one of the four enumerated statutory categories and do not recite any physical steps, (2) the claims are directed to the judicial exception category of a mental process, (3) the claims do not recite additional elements that integrate the alleged judicial exception into a practical application and that the claims do not recite any physical steps, and (4) the claims do not recite additional elements that amount to significantly more than any alleged judicial exception.

Applicant submits that: (1) all of the claims are directed to the statutory category of a process (Step 1 of the 101 Analysis) and that they do recite physical steps, (2) none of the claims are "directed to" the judicial exception category of a mental process because the claims cannot be practically performed in the human mind (with or without the assistance of pen and paper) (Step 2A of the 101 Analysis), (3) the claims do not "recite" a judicial exception, as they neither "set forth" nor "describe" an abstract idea, law of nature, or natural phenomenon (Step 2A Prong One of the 101 Analysis), (4) the claims recite additional elements that integrate any alleged judicial exception into a practical application for at least the reason that they provide for improvements to a technical field (Step 2A Prong Two of the 101 analysis), and (5) the claims recite additional elements that amount to significantly more than any alleged judicial exception for at least the reason that they set forth elements that are not well-understood, routine, or conventional. Applicant respectfully submits that the claims are subject matter eligible at every step of the *Alice/Mayo* framework and the revised analysis provided in the "October 2019 Patent Eligibility Guidance Update".

1. Step 1 of the 101 Analysis – All of the claims are directed to the statutory category of a process.

For step 1 of the 101 analysis, the Office appears to state that claims 10-19 are not directed to a statutory category because the term "obtaining" in these claims would not require any physical step. Applicants respectfully disagree with the Office's characterization of this element of the claims.

As recited in claim 10, the first set of sequence reads and the second set of sequence reads are obtained, "…by **sequencing** nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules…" (emphasis added). The obtaining of step (a) of claim 10 clearly and unequivocally recites a physical step, as "sequencing" is a biological reaction requiring the use and manipulation of tangible elements (such as, for example, sequencing reagents, nucleic acids from biological samples, an apparatus or vessel for the reaction to occur in, as well as other tangible elements required for a sequencing reaction known in the relevant art). Applicant further notes that the Office characterizes the similar 'obtaining' step of claim 20 as a physical step. Specifically, "[i]n the instant case, claims 20-25 have an additional element of '**obtaining**' **which requires a physical step to create the sequence read data**." (Office Action dated 4-11-2022, p. 10, paragraph 2 (emphasis added)). Applicant submits that, similar to claims 20-25, independent claim 10 and claims dependent thereof are directed to the statutory category of a process.

2. Step 2A of the 101 Analysis – None of the claims are directed to the judicial exception category of a mental process.

In the office action dated April 11, 2022, the Office alleges that, "[f]or step 2A of the 101 analysis, the judicial exception of the claims are the steps of accessing and analyzing sequence data for differences/variants…. **Here, the claims do not require a computer, or any large amount or complexity of read sequence data, and could be performed on paper and the analysis could be performed in one's mind** by comparing two sequences to see if there is any variant base between the two." (Office Action dated 4-11-2022, paragraph spanning pages 9 to 10 (emphasis added)). Applicant respectfully disagrees.

Applicant initially notes that the analysis performed by the Office at Step 2A of the 101 analysis appears to be inappropriate as it does not follow the two-prong analysis recited in the "October 2019 Patent Eligibility Guidance Update" issued October 17, 2019, referred to herein as "2019 Guidance Update". Specifically, the Office does not appear to have given any consideration to Step 2A Prong One. In the response to the previous office action dated February 28, 2022, Applicant provided arguments supporting the finding of subject mater eligibility at Step 2A Prong One (See page 8 of Applicant's previous Response dated 3-29-2022). Applicant maintains that the present claims fulfill the requirements for subject matter eligibility at Step 2A Prong One and has reiterated and expanded upon these explanations for subject matter eligibility in the subsequent subsection.

In order to provide a complete response to the office action, Applicant submits that none of the claims recite the judicial exception category of a mental process, because they cannot practically be performed in the human mind. In the "2019 Guidance Update", it is noted that, "[a] claim with limitation(s) that **cannot practically be performed** in the human mind **does not recite a mental process**." (2019 Guidance Update, page 7, heading (i) (emphasis added)). The relevant analysis is not whether a person having ordinary skill in the art could perform the processes in their mind, with or without the assistance of pen and paper, but whether the processes can be **practically** performed in the human mind.

Reading the claim as a whole, a human mind could not **practically** perform the recited method. To illustrate this point, it is first noted that paragraph [0178] of the specification teaches that individual nucleic acid template molecules can range from at least about 100 bases to at least about 500,000 bases (500 kb). Both independent claims 10 and 20, as well as dependent claims thereof, require the extraction of nucleic acid molecules. Paragraph [0076] of the specification teaches that multiple reads are acquired during a sequencing reaction, ranging from at least 2 to more than 10,000 reads. Both independent claims 10 and 20, as well as dependent claims thereof, require more than one sequencing reaction. Both of these factors are further amplified by the number of samples and/or fractionated components of a sample recited in the claims. After the sequencing reactions are performed, a comparative analysis of the data generated must be performed. A person could not realistically perform each of the operations of the claims for this amount of data. Therefore, Applicant submits that the claims are not directed to the judicial

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exception category of a mental process because the elements of the claims cannot practically be performed in the human mind (with or without the assistance of pen and paper).

3. Step 2A Prong One of the 101 Analysis – None of the claims recite an abstract idea, law of nature, or natural phenomenon.

As noted above, upon review of the office action dated April 11, 2022, it does not appear that the Office has directly addressed the Step 2A Prong One arguments put forth in Applicant's response filed on March 29, 2022. Applicant previously submitted, and continues to maintain the position, that none of the claims recite an abstract idea, law of nature, or natural phenomenon. As noted above, and in Applicant's response dated March 29, 2022, independent claims 10 and 20 recite tangible elements and nowhere recites a judicial exception. The Office states that the claims "…fall into the category of Mental Processes…" (Office Action dated 4-11-2022, p. 10, paragraph 1). As noted in the 2019 Guidance Update, a claim *recites* a judicial exception when the judicial exception is "set forth" or "described" in the claim (2019 Guidance Update, p. 1, underneath the heading "Meaning of "Recites""). Applicant submits that the claims do not "set forth" or "describe" a judicial exception because a human mind could not **practically** perform the recited methods, and therefore the claims do not recite a judicial exception.

Accordingly, Applicant submits that independent claims 10 and 20, as well as dependent claims thereof, should be found to be subject matter eligible at Step 2A Prong One.

4. Step 2A Prong Two of the 101 Analysis – Independent claims 10 and 20 recite additional elements that integrate the alleged judicial exception into a practical application.

Applicant again submits that, although the claims should be found patent eligible under Step 2A Prong One, independent claim 10 and independent claim 20 (and dependent claims thereof) also satisfy Step 2A Prong Two because the claims recite additional elements that integrate the alleged judicial exception into a practical application. In the office action dated April 11, 2022, the Office initially states that "[w]ith respect to the additional elements, it is noted that claim 10 does not necessarily require any physical steps…" (Office Action dated 4-11-2022, paragraph spanning pages 13-14). As noted above in response to Step 1 of the 101 analysis, independent claims 10 and 20, as well as dependent claims thereof, require, *inter alia*, a sequencing reaction. The obtaining of step (a) of claim 10 and the obtaining of step (e) of claim

20 clearly and unequivocally recites a physical step, as "sequencing" is a biological reaction requiring the use and manipulation of tangible elements.

The April 11th office action continues, "With respect to the judicial exception and analysis of the read data obtained, the fact pattern provided in *McRO* appears different from that of the instant claims. Here, the analysis steps are not integrated into a process like that of *McRO* that addressed a problem previously addressed manually, but rather applies steps that simply analyze data that is obtained." (Office Action dated 4-11-2022, paragraph spanning pages 13-14). It appears that the Office is taking a literal approach in the comparison of the claims of the application under review and the claims in the *McRO* case. However, as initially noted in Applicant's previous Response dated March, 29, 2022, the 2019 Guidance Update states on page 11 paragraph 2 that, "…the evaluation of Prong Two require the use of considerations (e.g., improving technology…) identified by the Supreme Court and the Federal Circuit to ensure that the claims as a whole "integrates [the] judicial exception into a practical application [that] will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception…"" (quoted initially in Applicant's previous Response dated 3-29-2022, page 9, first paragraph underneath the heading Step 2A Prong Two). Within the MPEP, the *McRO* case is provided as an example of claims that improve technology and are not directed to a judicial exception (See MPEP § 2106.04(d)(1) and MPEP § 2106.05(a)(II)).

Applicant previously submitted and maintains the position that, similar to *McRO*, the methods of independent claims 10 and 20, as well as dependent claims thereof, present improvements in the technical field of cancer diagnostics at least because the methods yield an improved detection of a tumor or cancer in a subject only requiring an initial tissue sample. The claimed methods allow for downstream monitoring and detection of a tumor or cancer in a subject without invasive sampling, further underscoring the improvements to the technical field of cancer diagnostics. As noted in the MPEP, "[t]he specification need not explicitly set forth the improvement, but it must describe the invention such that the improvement would be apparent to one of ordinary skill in the art..." and "[t]he claim itself does not need to explicitly recite the improvement…" (See MPEP § 2106.04(d)(1)). Applicant submits that a person of ordinary skill in the art would, "…recognize the claimed invention as providing an improvement" as set forth in MPEP § 2106.04(d)(1).

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Accordingly, Applicant submits that independent claims 10 and 20 and dependent claims thereof should further be found to be subject matter eligible at Step 2A Prong Two.

5. Step 2B of the 101 Analysis – Independent claims 10 and 20 recite additional elements that amount to significantly more than any alleged judicial exception.

Applicant again submits that, although the claims should be found patent eligible under Step 2A Prong One and/or Step 2A Prong Two, independent claim 10 and independent claim 20 (and dependent claims thereof) also satisfy Step 2B, because the claims include elements that are not well-understood, routine, or conventional. The Office states, "[i]n review of the evidence of record and given the breadth of the claims, there does not appear to be additional steps that are recited in the instantly claimed invention that would amount to significantly more than obtaining read data for analysis within the judicial exception," (Office Action dated 4-11-2022, page 11, paragraph 2) and that, "… neither the specification nor the claims provide a new means for comparing sequences or identifying variant as generically provided, and reporting as a final step broadly provides for indicating what the results were if any were identified." (Office Action dated 4-11-2022, paragraph spanning pages 13-14). Applicant respectfully disagrees with the Office's assertion that the claims do not provide additional elements that amount to "significantly more than obtaining read data for analysis".

As summarized in the MPEP, the Supreme Court has identified a number of considerations as relevant to the evaluation of whether elements of a claim qualify as "significantly more" than an alleged judicial exception (See MPEP § 2106.05(I)(A)). In addition to the "improvements to any other technology or technical field" consideration noted above the Step 2A Prong Two response, another consideration set forth is whether an element of a claim is well-understood, routine, or conventional (See MPEP § 2106.05(I)(A)(v)). Applicant continues to maintain the position that the claims include elements that are not well-understood, routine, or conventional (See page 10, last paragraph of Applicant's previous Response dated 3-29-2022). For example, it is not routine or conventional to "…obtain[] a first set of sequence reads and a second set of sequence reads by sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules…**using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said tissue sample of said subject in said first set of sequence reads that**

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is not present in said second set of sequence reads…**identifying said one or more first mosaic variants specific to said tissue sample of said subject in a first additional sample of said subject, wherein said first additional sample is obtained from a source and at a time point that is different than said tissue sample**…and…**providing a report based on an identification of said one or more first mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer**…," as recited in claim 10 (emphasis added). Further, it is not routine or conventional to "…obtain[] a first set of sequence reads and a second set of sequence reads generated by sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules… **identifying said one or more first mosaic variants specific to said subject in a second sample of said subject, wherein said second sample is obtained from a source or at a time point that is different than said blood sample**…and…**providing a report based on an identification of said one or more first mosaic variants specific to said subject in said second sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition**…," as recited in claim 20. These elements are not present in any of the eight references that the Office has provided to support the assertion that the claim is obvious. While the obviousness rejection is not directly relevant to the 101 analysis, the fact that none of the eight references provides for these elements of the claims supports Applicant's arguments that the claims recite additional elements that are not routine or conventional, and therefore amount to significantly more than any alleged judicial exception.

The Office's response continues that, "…the specification provides no new correlations of disease based on obtaining read data…it was readily known that certain genetic alterations were known to be associated with the progression of cancer, as well as alterations associated with other conditions and diseases…," and that,"…the present claims broadly provide for known steps of isolating two known sources of DNA in blood, and using leukocytes as a control which was also taught (by Lo et al)." (Office Action dated 4-11-2022, page 14, 1st paragraph). Applicant disagrees with the Office's characterization of the claims and the specification. As noted in the preceding paragraph, independent claims 10 and 20, as well as their dependent claims, recite elements that are not well-understood, routine, or conventional. The present claims are fully supported throughout the specification as previously noted in the Applicant's previous

Response dated March 29, 2022, and in the present response to the office action dated April 11, 2022. Therefore, Applicant submits that, when viewed as a whole instead of the individual parts, the specification and the present claims provide more than known "correlations of disease based on obtaining read data" and "steps of isolating two known sources of DNA in blood".

Accordingly, Applicant submits that independent claims 10 and 20, and dependent claims thereof, should further be found to be subject matter eligible at Step 2B.

In summary, at every step of the *Alice/Mayo* framework and the revised analysis provided in the 2019 Guidance Update, the claims should be found to be subject matter eligible. The claims are directed to the statutory category (of a process) as required by Step 1 of the analysis. For Step 2 of the analysis, the claims: (1) do not "recite" a judicial exception (Step 2A Prong One), (2) are not "directed to" a judicial exception (Step 2A Prong Two), and (3) recite "significantly more" than any alleged judicial exception (Step 2B). In view of the foregoing, Applicant submits that claims 10-25, as amended herewith, are in compliance with 35 U.S.C. § 101. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 101 be withdrawn.

E. Rejection under 35 U.S.C. § 103

The Office maintains its rejection of claims 10-23 and rejects newly added claims 24-25 under 35 U.S.C. 103 as allegedly being unpatentable over Lo et al. (1997) ("Lo"), De Mattos-Arruda et al. (2013) ("De Mattos-Arruda"), Laktionov et al. (2004) ("Laktionov"), Ellinger et al (Urologic Oncology 29:124-129 (2011)) ("Ellinger"), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)) ("Jung"), Shaw et al. (Genome Research 22:220-231 (2012)) ("Shaw"), Lewis et al. (US 2012/0058480 Al) ("Lewis"), and Green et al. (US 2005/0260645 Al) ("Green").

1. The combination of the references does not teach all elements of the present claims.

Without conceding to the basis of the rejection, and solely to expedite the prosecution of this application, Applicant has amended independent claims 10 and 20 to clarify certain differences over the asserted combination of Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung,

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Shaw, Lewis, and Green. Applicant submits that the claims as amended are not obvious in view of Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green, because none of the references, alone or in combination, teaches or discloses all of the elements of independent claims 10 and 20.

For example, nothing in Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, or Green teaches or discloses, or even suggests, "A method of analyzing a biological sample obtained from a subject being screened for a cancer, wherein the biological sample is from a non-fetal source, the method comprising…**using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said tissue sample of said subject** in said first set of sequence reads that is not present in said second set of sequence reads…**identifying said one or more first mosaic variants specific to said tissue sample of said subject in a first additional sample of said subject**, wherein said first additional sample is obtained from a source and at a time point that is different than said tissue sample...and…**providing a report based on an identification of said one or more first mosaic variants specific to said tissue sample of said subject in said first additional sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a cancer in said subject**," as recited in claim 10 (emphasis added).

Further, nothing in Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, or Green teaches or discloses, or even suggests, "A method for early disease detection in a subject using at least two samples from the subject, wherein the at least two samples are from a non-fetal source, said method comprising…**using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants specific to said subject** in said first set of sequence reads that is not present in said second set of sequence reads…**identifying said one or more first mosaic variants specific to said subject in a second sample of said subject**, which second sample is obtained from a source or at a time point that is different than said blood sample…and…**providing a report based on an identification of said one or more first mosaic variants specific to said subject in said second sample, wherein said report comprises predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in said subject**," as recited in claim 20.

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Claims 11-19 depend from and include all of the elements of claim 10 and recite additional elements of particular advantage and utility. Claims 21-25 depend from and include all of the elements of claim 20 and recite additional elements of particular advantage and utility. As such, the asserted combination of Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green also fails to render the present claims obvious.

As noted in Applicant's prior response, the "providing a report" elements of independent claim 10 step (d) and independent claim 20 step (h) are not disclosed in any of the references (see paragraph 3 of p. 12 and paragraph 2 of p. 13 of Applicant's prior Response dated 3-29-2022). In the present office action, the Office alleges that, "Clearly Lo et al. provide reporting and expectations of what might be observed for cfDNA representing a fetus….Further, given the teachings of Mattos-Arruda et al. and Laktionov et al. for the presence and correlation of markers that could be detected, it appears obvious that known correlations could be used and applied to reporting based on the information that results from the analysis of the read data of cfDNA versus a control." (Office Action dated 4-11-2022, pages 17-18).

Applicant maintains the position that none of the references, alone or in combination, teach the "providing a report" element as previously put forth in Applicant's prior Response dated March 29, 2022. In the present office action, the Office states, "[w]ith respect to the amendment for an additional step of d) for providing a report, a review of the specification suggests that there is no new means for reporting, and that broadly this step and limitation provides for reporting what was observed as a form of data." (Office Action dated 4-11-2022, page 17, paragraph 1). Applicant respectfully disagrees with the Office's characterization of this element of the claims and the specification. As noted above, Applicant has further amended the "providing a report" element of claim 10 step (d) and the "providing a report" element of claim 20 step (h) to clarify certain differences over the cited references. The "providing a report" element of claim 10 step (d) and "providing a report" element of claim 20 step (h) do not just, "…provid[e] for reporting what was observed as a form of data", as asserted by the Office. The "providing a report" element in claim 10 integrates the results of the comparative analysis of sequence reads to identify mosaic variants specific to the tissue sample of the subject, as set forth in steps (b) and (c) of claim 10, and further comprises, "…predicting, diagnosing, and/or prognosing a status or outcome of a cancer in [the] subject." The "providing a report" element in

claim 20 integrates the results of the comparative analysis of sequence reads to identify mosaic variants specific to the subject, as set forth in steps (f) and (g) of claim 20, and further comprises, "…predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in [the] subject." Applicant does not acquiesce to the basis of the rejection, but rather has further amended the claims in a good faith effort to further prosecution of the current application. Applicant submits that none of the references, alone or in combination, teach the "providing a report" element of claim 10 step (d), nor do they teach the "providing a report" element of claim 20 step (h).

Applicant notes that the Office does not point to any specific section of the Lo, De Mattos-Arruda, or Laktionov references that discloses the "providing a report" elements of independent claim 10 step (d) or independent claim 20 step (h) as previously presented. As stated in the MPEP, "…When a reference is complex or shows or describes inventions other than that claimed by the applicant, the particular part relied on must be designated as nearly as practicable." (See 37 CFR § 1.104(c)(2)). As discussed above, the clarification provided in the currently pending claims further details distinctions that are not taught in any of the cited references, either individually or when the teachings are combined.

2. There is no reasonable expectation of success in the combination of the Lo reference with the De Mattos-Arruda and Laktionov references.

In the present office action, the Office maintains an assertion that the claims are obvious and states that, "As further evidence of cfDNA representing the subject (i.e. non-fetal source) **Mattos-Arruda et al. and Laktionov et al. were provided for the teaching that circulating blood biomarkers promise to become non-invasive real-time surrogates for tumour tissue based biomarkers**….Together these references provide the basis that cfDNA in the blood represent cfDNA from the subject (non-fetal source) and that the cfDNA can serve as a biomarker for diseases that may be present in a subject." (Office Action dated 4-11-2022, pages 16-17 (emphasis added)).

As discussed above, Applicant submits that no combination of the cited references achieves the claimed invention. In addition, Applicant submits that there is no reasonable expectation of success in practicing the claimed invention based on the teachings of the cited

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references: "Where there is a reason to modify or combine the prior art to achieve the claimed invention, the claims may be rejected as *prima facie* obvious **provided there is also a reasonable expectation of success**." (See MPEP § 2143.02(i) quoting *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)) (emphasis added). It is further stated that, "[w]hether an art is predictable or whether the proposed modification or combination of the prior art has **a reasonable expectation of success is determined at the time the invention was made**." (See MPEP § 2143.02(iii) quoting *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986) (emphasis added)). Applicant submits that there is no reasonable expectation of success in combining the De Mattos-Arruda and/or Laktionov references with the Lo reference.

The Office states that, "Lo et al provide the basis of separation of cfDNA from leukocytes and their use as controls for the information that the sequence reads represent relative to different conditions and disease." (Office Action dated 4-11-2022, p.18, underneath the heading "Previous rejection of record"). Applicants submit that the De Mattos-Arruda and Laktionov references directly contradict the idea that circulating biomarkers could diagnose a disease, such as cancer, at the time of the present invention.

While the De Mattos-Arruda reference notes that, "[c]irculating blood biomarkers **promise to become** non-invasive real-time surrogates for tumour tissue-based biomarkers," there was no reasonable expectation of success at the time of the priority date of the presently claimed invention as evidenced by the fact that the De Mattos-Arruda reference consistently disparages the use of circulating biomarkers for the detection of diseases, such as cancer.

For example, the reference states that, "[a]lthough these tumour markers are useful for monitoring patients with metastases during therapy, **current evidence does not support their use for screening, diagnosing or post-operative surveillance after primary breast cancer**...**because of their limited sensitivity and specificity**." (De Mattos-Arruda, p. 378, column 2, paragraph 1 (emphasis added)). The reference also states that, "Owing to the small sample size and the fact that none of the patients had a relapse during the follow-up period, **further studies are required to determine whether this approach would be sufficiently sensitive** to be employed as a screening tool or for therapy response monitoring." (De Mattos-Arruda, p. 380, column 1, paragraph 2 (emphasis added)). Further, "[d]iscordance in the expression of ER, PR, and HER2 receptors has been observed among primary tumours,

metastatic deposits and circulating biomarkers…it should be emphasized that these discrepancies could at least in part be attributed to methodological issues. If the differences stem from methodological issues, **the analyses of circulating biomarkers might lead to suboptimal therapeutic management of patients** with breast cancer." (De Mattos-Arruda, p. 380, column 2, paragraph 3 (emphasis added)). The reference concludes by stating, "[d]espite the burgeoning breast cancer biomarker data, CTCs and **cfDNA have not yet been translated into standardized clinical tools** to assist the management of patients. **Better and more-robust methods are needed to study the molecular characteristics of tumours through the analysis of circulating biomarkers**…. Although technology is advancing quickly, and new avenues for detecting blood biomarkers are being developed, **we should be fully cognizant of the challenges of translating these promising research tools into clinically useful test**. Furthermore, **a thorough assessment of the parameters that impact on sample adequacy for the assessment of circulating biomarkers is warranted**." (De Mattos-Arruda, p. 386, column 2, full paragraph 2 (emphasis added)). Therefore, a person having ordinary skill in the art would have no reasonable expectation of success in combining the teachings of De Mattos-Arruda with the teaching of the Lo reference. To reiterate, the De Mattos-Arruda consistently disparages the utilization of circulating biomarkers for the detection of diseases and directly contradicts any assertion that a reasonable expectation of success can be found in the combination of the Lo reference (i.e., a reference that, according to the Office, allows for the detection of a disease using circulating biomarkers) with the De Mattos-Arruda reference.

With respect to the Laktionov reference, the Office states that, "…Laktionov et al. teach that both DNA and RNA can be identified and analyzed for method to diagnose cancer." (Office Action dated 4-11-2022, pages 16-17). As an initial matter, Applicant notes that the Laktionov reference examines *extracellular cell-surface-bound* nucleic acids in healthy donors, breast cancer patients, and patients with non-malignant tumors (Laktionov, p. 221, paragraph 1 through p. 222, paragraph 1), and does not provide the general teaching that "both DNA and RNA can be identified and analyzed for method to diagnose cancer," asserted by the Office. This distinction is important as the Laktionov reference explicitly contradicts the Office's assertion. In relevant part, the reference states, "…quantification of plasma and cell-surface-bound ex[tracellular] N[ucleic] A[cids] can be used as a screening assay, as a part of a general health checkup for men, whereas **a more specific assay for tumour-related DNA is necessary for cancer diagnostics**."

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(Laktionov, p. 225, paragraph 3 (emphasis added)). Similar to the De Mattos-Arruda reference, there is no reasonable expectation of success in combining the Lo reference with the Laktionov reference, which teaches that a more specific assay is necessary to diagnose cancer.

In view of the foregoing, Applicant submits that claims 10-25, as amended herewith, are in compliance with 35 U.S.C. § 103. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

F. Conclusion

For at least the reasons set forth above, it is submitted that claims 10-29 are in condition for allowance. A Notice of Allowance is earnestly solicited.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

The Applicants reserve the right to pursue at a later date any previously pending or other claims that capture any subject matter supported by the present disclosure. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have disclaimed or disavowal any subject matter supported by the present application.

Except for issues fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees including fees due under 37 CFR § 1.16 and 1.17, which may be required, and including any required extension of time fees, or credit any overpayment to Deposit Account 15-0665 (Docket Reference: 48929.4008/US03).

Respectfully submitted,

Orrick, Herrington & Sutcliffe LLP

Dated: 8-4-2022

By: /Alex Straughn/
Alex Straughn, Reg. No. 80,155, for
Gargi Talukder, Reg. No. 61,368

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Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Telephone: (949) 567-6700
Facsimile: (949) 567-6710

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/494,513	Filing Date 10/05/2021	☑ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	08/04/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/ANGELA D JOHNSON/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	

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1631	

NOTIFICATION DATE	DELIVERY MODE
04/11/2022	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
jmichel@orrick.com
vsantos@orrick.com

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Office Action Summary	Application No. 17/494,513	Applicant(s) West, John	
	Examiner Joseph T Woitach	Art Unit 1631	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 3/29/2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 10-25 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) 10-25 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

TrackOne Request

Applicants request filed 10/5/2021 was been granted (see paper mailed 12/8/2021).

Applicant's response filed 3/29/2022 to the first action on the merits mailed 2/28/2022 did not require an extension of time.

Applicant's Amendment

Applicant's amendment filed 3/29/2022 has been received and entered. Claims 1-9 were previously cancelled, claims 10, 12 and 20 have been amended and claims 24-25 have been added.

Claims 11-25 are pending.

Election/Restriction

Applicant's election without traverse of Group II, and the species of a blood sample and SNPs in the reply filed on 2/9/2022 was acknowledged.

It was noted that upon search and review of the specification it does not appear to be a burden to examine both groups as Group I appears to comprise similar but broader steps that are required of the elected method for screening a patient for a disease; and similarly the type of genetic variant being analyzed/observed would also be known or associated with the disease being analyzed.

Accordingly, the restriction requirement **was withdrawn.**

Newly added claims 24-25 are dependent on the pending claims and appear consistent with the elected invention.

Claims 10-25 are pending and currently under examination as drawn to a method of analyzing a biological sample by comparing sequence reads obtained from a blood component and the comparison to samples taken at a different time from the first for patient screening are currently under examination.

Priority

This application filed 10/5/2021 is a Divisional of 16/132123, now US Patent 11142802, which is a continuation of 14/929075, now US Patent 10125399, which claims benefit to US provisional application 62/072936 filed 10/30/2014; and is related to 17/065406 filed 10/7/2020 through parent 16/132123, and to PCT/US15/58483 filed 10/30/2015.

No comment on the priority summary is provided by Applicants in the instant response.

Double Patenting

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).

Claims 10-23 rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of U.S. Patent No. 11142802 (16/132123 allowed 8/9/2021) **is withdrawn.**

The terminal disclaimer filed 3/29/2022 has been received and APPROVED (see paper entered 3/29/2022).

Claims 10-23 rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of U.S. Patent No. 10125399 (14/929075 allowed 10/24/2018) **is withdrawn.**

The terminal disclaimer filed 3/29/2022 has been received and APPROVED (see paper entered 3/29/2022).

Claims 10-23 provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 10-17, 1924, 27, 29-33 of copending Application No. 17/065406 (RCE filed 1/28/2022) **is withdrawn.**

The terminal disclaimer filed 3/29/2022 has been received and APPROVED (see paper entered 3/29/2022).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-25 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for applications subject to pre-AIA 35 U.S.C. 112, the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the newly added limitation of excluding a blood sample from a non-fetal source is considered a new limitation not specifically contemplated in the present disclosure.

Applicants note support for the current amendments. Initially it is noted that in reviewing the teachings of the specification as a whole and at [0016], it appears to provide adequate support for newly added step d) and providing a report as an additional step, for example at:

"In some embodiments, the state is determined by comparing a nucleic acid sequence or portion thereof to a reference to determine an apoptotic pattern, necrotic pattern, or predetermined mutations. In some embodiments, the reference is a genome of the subject. In some embodiments, ***the method further comprises providing a report and/or a therapeutic intervention based on a determination of the state of health.***"

However, in reviewing the teachings of [0058], it does not appear to provide support for newly added limitation 'from a non-fetal source' but rather at [0058] for analyzing a tumor versus normal and identifying mosaic variants in the cfDNA as provided:

"The method may also be used to perform ***tumor vs normal analysis*** without a tissue specimen from the tumor, and thus can be used to identify specific variants in the tumor and to recommend specific anti-cancer drugs based on the mutation to be targeted. The normal analysis may be performed on white blood cells (i.e., leukocytes) prior to the development of the tumor. In some cases, the normal analysis and the tumor analysis are performed on a single blood sample. In this case, whole blood can be collected and centrifuged to separate the plasma which contains the cfDNA, the buffy coat which contains the white blood cells, and the red blood cells. Nucleic acids can be extracted from the plasma and the white blood cells and sequenced. In some cases, the cfDNA may contain distal nucleic acids that originated from a tumor. In these cases, tumor variants may be identified by identifying ***mosaic variants in the cfDNA*** that are not represented in the white blood cells ("normal"). In some cases, the tumor variants are causal variants (i.e., tumor-causing)."

A review of the specification as a whole appears to support that the inclusion of fetal sources is contemplated not excluded as presently claimed, for example in [0140] listing a series of diseases including 'erythroblasosis fetalis' and more generally in [0143] teaching:

"The methods as disclosed herein may be ***used for monitoring the health of a fetus*** using whole or partial genome analysis of nucleic acids derived from a fetus, as compared to the maternal genome. For example, nucleic acids can be useful in pregnant subjects for fetal diagnostics, with fetal nucleic acids serving as a marker for gender, rhesus D status, fetal aneuploidy, and sex-linked disorders. The methods as disclosed herein may identify fetal mutations or genetic abnormalities. The methods as disclosed herein can enable detection of extra or missing chromosomes, particularly those typically associated with birth defects or miscarriage. The methods as disclosed herein may comprise, or comprise the use of, the diagnosis, prediction or monitoring of autosomal trisomies (e.g., Trisomy 13, 15, 16, 18, 21, or 22) and may be based on the detection of foreign molecules. The trisomy may be associated with an increased chance of miscarriage (e.g., Trisomy 15, 16, or 22). Alternatively, the trisomy that is detected is a livebom trisomy that may indicate that an infant will be born with birth defects (e.g., Trisomy 13 (Patau Syndrome), Trisomy 18 (Edwards Syndrome), and Trisomy 21 (Down Syndrome)). The abnormality may also be of a sex chromosome (e.g., XXY (Klinefelter's Syndrome), XYY (Jacobs Syndrome), or XXX (Trisomy X). The methods disclosed herein may comprise one or more genomic regions on the following chromosomes: 13, 18, 21, X, or Y. For example, the foreign molecule may be on chromosome 21 and/or on chromosome 18, and/or on

chromosome 13. The one or more genomic regions may comprise multiple sites on multiple chromosomes. [0144] Further fetal conditions that can be determined based on the methods herein include monosomy of one or more chromosomes (X chromosome monosomy, also known as Turner's syndrome), trisomy of one or more chromosomes (13, 18, 21, and X), tetrasomy and pentasomy of one or more-50- chromosomes (which in humans is most commonly observed in the sex chromosomes, e.g., XXXX, XXYY, XXXY, XYYY, XXXXX, XXXXY, XXXYY, XYYYY and XXYYY), monoploidy, triploidy (three of every chromosome, e.g., 69 chromosomes in humans), tetraploidy (four of every chromosome, e.g., 92 chromosomes in humans), pentaploidy and multiploidy."

which appears to provide that the sample contain cfDNA of a fetus. More generally, the specification does appear to provide for a source that the subject is not a fetus, however it does not appear to exclude that the sample itself not contain a fetal source of cfDNA, nor does the specification provide guidance on how to remove fetal cfDNA or how to discriminate between a fetal or subject cfDNA in a blood sample.

Dependent claims are included in the basis of the rejection because they fail to clarify or address the issue. For example, claim 14 provides for a third sample which includes the listing of 'breast milk sample' which implies that subject is or was pregnant and that fetal cfDNA may be present in the blood of a subject. More clearly setting forth a sample source and method steps consistent with the present disclosure would address the basis of the rejection.

> The following is a quotation of 35 U.S.C. 112(b):
> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.
>
> The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-25 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which the inventor or a joint inventor (or for applications subject to pre-AIA 35 U.S.C. 112, the applicant), regards as the invention. Claim 10 has been amended to recite the limitation of 'separated from a blood sample of said subject from a non-fetal source' and it is unclear if the subject to be excluded should not be a fetus, or that the blood sample not contain fetal material and that the fetal source not exist or is somehow separated from other sources that may be present in the blood sample that is obtained.

More clearly setting forth the nature of the sample, the specific extraction steps that differentiate the two sources that may be present in blood, or limitations consistent with the specification for how sequences are obtained in step a) to differentiate the two sources would address the basis of the rejection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10-23 **stand** rejected **and newly added claims 24-25 are rejected** under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter because the claimed invention is not directed to patent eligible subject matter. Based upon an analysis with respect to the claim as a whole, claims 10-25 do not recite something significantly different than a judicial exception. The rationale for this determination is explained below.

Claim analysis

Independent claims 10 and 20 have been amended and still are directed generally towards a method of detecting variants in circulating cell free DNA as compared to a reference of

leukocytes present in the blood of a patient. The claims have been amended to indicate that the blood is not from a fetus and that the final step provides for a report of any identification of a variant. The claim sets forth the steps of obtaining blood from a subject, and separating into two parts one representing leukocytes and one representing the remaining portion of the blood sample that has cfDNA, obtaining reads of the nucleic acids reads that are present in the samples by sequencing the nucleic acids that are present, and comparing the sequence data identifying possible variants that may be present between the two where the reads from the leukocytes is to be designated 'normal' in the analysis. Dependent claims set forth the types of variations that might be detected, such as copy number, SNPs, MNPs, inDels,.. or that the variant is associated with disease and/or possible treatment and that the method steps can be performed more than once at different time points for comparison of the variants at different times. Newly added claims provide that instructions for intervention is provided based on what variant might be observed, and a listing of the types of variants that might be observed when comparing the read data (similar to dependent limitations for claim 10 set forth in claims 12 and 15).

For step 1 of the 101 analysis, claims 20-25 are found to be directed to a statutory category of a process. For claims 10-19, it appears that these claims are not directed to a statutory category, because while setting forth a process the steps all appear to be directed to instructions for analyzing read data. While claim 10 recites 'obtaining', in review of the specification for excluding or identifying fetal sources of reads as amended, it appears that this step can be through analysis of the reads and does not require any physical step. Here, the reads can be obtained from a file of information previously provided.

For step 2A of the 101 analysis, the judicial exception of the claims are the steps of accessing and analyzing sequence data for differences/variants. The step of aligning and

comparing sequence to arrive at the identification of variations between sequences are considered instructional steps. In view of the specification, the claim requires analyzing homology or computing similarity scores to determine differences in the sequences. The judicial exception is a set of instructions for analysis of sequence data, and appears to fall into the category of Mental Processes that is concepts performed in the human mind (including an observation, evaluation, judgment, opinion). Here, the claims do not require a computer, or any large amount or complexity of read sequence data, and could be performed on paper and the analysis could be performed in one's mind by comparing two sequences to see if there is any variant base between the two. Dependent claims recite comparison of a third source and that multiple variants might be detected, but similar to comparing two sequences it does not appear beyond observation to align and identify differences among sequences and call them variants. For the additional step of providing a report, in review of the specification this generically and broadly provides for reporting what differences were observed.

Recent guidance from the office requires that the judicial exception be evaluated under a second prong to determine whether the judicial exception is practically applied. In the instant case, claims 20-25 have an additional element of 'obtaining' which requires a physical step to create the sequence read data. This judicial exception requires steps recited at high level of generality and is not found to be a practical application of the judicial exception as broadly set forth, and provides for known combination of steps used in obtaining sequence read data (see also present specification for generalized listing of possible methods that can be use in the context of the steps). With respect to providing sources from blood that include separation of leukocytes and the remaining cfDNA, and further analysis and comparison of the two, Lo et al. (1997) provide specific method steps for separating and comparing the two nucleic acid sources

present in a blood sample. When the steps are viewed as physical steps or additional elements, it appears that the steps of obtaining sequence data/information and subsequently analyzing read data are separate from one another, and do not integrate back into the steps comprising additional elements. As amended, the claims now require providing a report however this appears to be generically directed to reporting the observation of the possible differences/variants between the aligned sequences that were observed. In this analysis, it appears that the step of obtaining sequence information is not integrated with the judicial exception and only provides the instruction to report what is observed, nor do the claims provide a practical application of the broad steps used to obtain sequence reads as a consequence of the analysis (as provided in the fact pattern in *Vanda*) for what is done with the information in a report.

For Step 2B of the two step analysis, one is to determine whether any element or combination of elements, in the claim is sufficient to ensure that the claim as a whole amounts to significantly more than the judicial exception. In review of the evidence of record and given the breadth of the claims, there does not appear to be additional steps that are recited in the instantly claimed invention that would amount to significantly more than obtaining read data for analysis within the judicial exception. In this case the judicial exception is the information of where a given read aligns with a normal or reference sequence to potentially identify variations between reads. More specifically, it is noted that at the time of filing that using circulating cell free DNA was known and used for diagnostic methods and used for cancer intervention (see for example the teachings of Lo et al., De Mattos-Arruda et al. and Laktionov et al.) and are considered as known and conventional steps of obtaining and separating nucleic acids in a sample and obtaining genetic information about a patient. As such, the instant claims are drawn only to an abstract process that only manipulates genetic data and the judicial exception of a natural

phenomenon (identification of variant sequences in circulating cell free DNA versus a tissue), and are not directed to statutory subject matter. Dependent claims that set forth the use of an array or bead to capture specific sequences or the use of amplification to provide greater copy number for sequence analysis for analysis in the judicial exception, do not appear to be novel and appear to be a conventional means for 'enriching' or 'capturing' a sequence of interest (claims 20-24) from a sample as a step of isolation or purification consistent with the disclosure of the present specification. Therefore the result of the analysis is that the claims are directed towards a judicial exception, i.e. an abstract idea. In the instant case, the claims are directed to only the analysis and manipulation of data.

Without additional limitations, a process that employs mathematical algorithms or general considerations to manipulate existing information (in this case defining the presence/absence of variants/alleles in a mixed sample) to generate additional information (in this case describing the nucleic acids present in a sample) is not patent eligible. Furthermore, if a claim is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is non-statutory. In other words, patenting abstract ideas cannot be circumvented by attempting to limit the use [the idea] to a particular technological environment. For the instant claims, it is noted that a computer and/or program/product can be used to compare sequence reads for homology or variation (specification provides guidance for available tools), but this amount to mere instruction to implement an abstract idea in a computer environment. The hardware contemplated in the specification for the analysis do not offer a meaningful limitation beyond generally linking "the use of the method to a particular technological environment,' that is, implementation via computers." see Alice Corp v. CLS Bank Int'l 573 U.S. (2014). For the reasons set forth above, the claims are not

considered to recite something significantly different than a judicial exception and thereby are not directed to patent eligible subject matter.

Response to Applicant's arguments

Applicants provide a summary of guidance relative to the analysis required for 101, highlighting the points for the claims being directed to a statutory category and guidance that judicial exception that provide a practical application under step 2A should be found patent eligible and provide an explanation for example of that in the *McRO* decision. Reciting the limitations of the claims, Applicants argue like in *McRO* the method provides rules to analyze a biological sample and screen for disease. Applicants further note that claim 20 provides for physical steps for the isolation and sequencing of DNA. Under Step 2A prong 2 Applicants argue that the claims provide additional elements that integrate the judicial exception into a practical application. Similar to McRO, where here the analysis is performed using a single blood sample, where the sample contains leukocytes that serve as a control and cfDNA which may contain DNA from other cells that might contain variants relative to a control, for example mutations and variants present in cancer cells. Applicants arguments and claim amendments have been fully considered, but not found persuasive.

With respect to the additional elements, it is noted that claim 10 does not necessarily require any physical steps, and that obtaining given the guidance of the specification provides for obtaining read data. The steps considered additional elements for isolating and sequencing DNA from a blood sample have been acknowledged, and Lo et al has been cited and discussed that this step was known and practiced in the prior art, and for the same purpose of comparing cfDNA to leukocytes as a control. With respect to the judicial exception and analysis of the read data obtained, the fact pattern provided in *McRO* appears different from that of the instant claims.

Here, the analysis steps are not integrated into a process like that of *McRO* that addressed a problem previously addressed manually, but rather applies steps that simply analyze data that is obtained. It is noted that neither the specification nor the claims provides new means for comparing sequences or identifying variants as generically provided, and reporting as a final step broadly provides for indicating what the results were if any were identified. Clearly the art of record demonstrates that methods of isolating cfDNA from leukocytes was known and practiced, and that variations in the reads between the two could be observed. Further, the specification provides no new correlations of disease based on obtaining read data, and it was readily known that certain genetic alterations were known to be associated with the progression of cancer, as well as alterations associated with other conditions and diseases all of which the present claims and disclosure rely upon to practice the claims as broadly set forth. Unlike the fact pattern in *McRO* which provided an automated set of rules that addressed a problem previously resolved manually, the present claims broadly provide for known steps of isolating two known sources of DNA in blood, and using leukocytes as a control which was also taught (by Lo et al). Given the evidence of record and breadth of the claims, Applicant's arguments that the steps provide an improvement and significantly more do not appear to be consistent with the fact pattern and evidence of record that the claims are patent eligible as provided in *McRO*. Further, given the evidence of record, the art provides that read data could be observed and could be correlative to diseases such as cancer. Therefore, for the reasons above and of record, the rejection **is maintained**.

As noted previously, one way to overcome a rejection for non-patent-eligible subject matter is to persuasively argue that the claimed subject matter is not directed to a judicial exception. Another way for the applicants to overcome the rejection is to persuasively argue that

the claims contain elements in addition to the judicial exception that either individually or as an ordered combination are not well understood, routine, or conventional. Another way for the applicants to overcome the rejection is to persuasively argue that the claims as a whole result in an improvement to a technology. Persuasive evidence for an improvement to a technology could be a comparison of results of the claimed subject matter with results of the prior art, or arguments based on scientific reasoning that the claimed subject matter inherently results an improvement over the prior art. The applicants should show why the claims require the improvement in all embodiments.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 10-23 as amended **stand** rejected and **newly added claims 24-25 are** rejected under 35 U.S.C. 103 as being unpatentable over Lo et al. (1997), De Mattos-Arruda et al. (2013), Laktionov et al. (2004), Ellinger et al (Urologic Oncology 29:124-129 (2001)), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)), Shaw et al (Genome Research 22:220-231 (2012)), Lewis et al. (US 2012/0058480 A1) and Green et al. (US 2005/0260645 A1).

Response to Applicant's arguments and claim amendments

Applicants note the amendment to the claims providing steps i)-ii) and d) for clarification and argue that none of the references provide for a non-fetal source and fail to provide early disease diagnosis reporting, where the early reporting is based on detection of a variant when comparing cfDNA sequences to that of leukocytes used as a control reference sequence obtained from the subject. The claim amendments and Applicants arguments have been fully considered, but not found persuasive.

With respect to the amendments to the claims with respect to cfDNA 'from a non-fetal source' it is acknowledged that the teaching of Lo et al who provide the method steps for isolating cfDNA from leukocytes for sequencing and analysis/comparison focus on the analysis of cfDNA that is present from the fetus, however it would be readily known that the cfDNA in the sample also contained the maternal cfDNA and serves as a source of non-fetal cfDNA by itself. As further evidence of cfDNA representing the subject (i.e. non-fetal source) Mattos-Arruda et al. and Laktionov et al. were provided for the teaching that circulating blood

biomarkers promise to become non-invasive real-time surrogates for tumour tissue based biomarkers. In the basis of the rejection, it was specifically noted that Mattos-Arruda et al. teach that circulating biomarkers have been investigated as tools for breast cancer diagnosis, the dissection of breast cancer biology and its genetic and clinical heterogeneity, prognostication, prediction and monitoring of therapeutic response and resistance, and that Laktionov et al. teach that both DNA and RNA can be identified and analyzed for method to diagnose cancer. Together these references provide the basis that cfDNA in the blood represent cfDNA from the subject (non-fetal source) and that the cfDNA can serve as a biomarker for diseases that may be present in a subject. Lo et al provide the basis of separation of cfDNA from leukocytes and their use as controls for the information that the sequence reads represent relative to different conditions and diseases. Given the evidence of record, it appears that art provides that cfDNA present in the blood could be used to determine the presence of disease such as cancer (in additional to analysis of fetal DNA in a pregnant subject), and that methods for isolating and analyzing cfDNA versus leukocytes as a control were known and used. Given the teachings as a whole, it appears obvious that methods of isolation and analysis of cfDNA v. leukocytes, and that in non-pregnant subjects the cfDNA would represent the subject that is represent a non-fetal source are provided by the teachings of the cited references.

With respect to the amendment for an additional step of d) for providing a report, a review of the specification suggests that there is no new means for reporting, and that broadly this step and limitation provides for reporting what was observed as a form of data. Clearly Lo et al. provide reporting and expectations of what might be observed for cfDNA representing a fetus. Again, it is recognized by Lo et al. that variants of the maternal and paternal source of the information would be present and can be analyzed. Further, given the teachings of Mattos-

Arruda et al. and Laktionov et al. for the presence and correlation of markers that could be detected, it appears obvious that known correlations could be used and applied to reporting based on the information that results from the analysis of the read data of cfDNA versus a control.

A review of the arguments and evidence of record does not appear to provide for new methods of isolation or for reporting observations, or secondary considerations that comparing cfDNA to a control from a subject provides any unique result or requirement for analysis beyond aligning and comparing read data to observe potential differences. Further, it would have been expected that biomarkers correlated with a variety of conditions could be observed given the teachings of Mattos-Arruda et al. and Laktionov et al.

Therefore, for the reasons above and of record, the rejection **is maintained**.

Previous rejection of record

Lo et al provide a report for the presence of cfDNA in maternal plasma and serum, and note that the presence of tumor DNA has been found and analyzed in cancer patients. The methods disclosed by Lo et al. used a rapid-boiling method to extract DNA from plasma and serum. DNA from plasma, serum, and nucleated blood cells from 43 pregnant women underwent a sensitive Y-PCR assay to detect circulating male fetal DNA from women bearing male fetuses. More specifically, maternal human blood samples were processed 1–3 h after venesection. Blood samples were centrifuged at 3000 *g*, and plasma and serum were carefully removed from the nucleic-acid-containing and plain tubes, respectively, and transferred into plain polypropylene tubes. Great care was taken to ensure that the buffy coat or the blood clot was undisturbed when plasma or serum samples, respectively, were removed. After removal of the plasma samples, the red-cell pellet and buffy coat were saved for DNA extraction with a Nucleon DNA extraction kit. The plasma and serum samples then underwent a second centrifugation at

3000 *g*, and the re-centrifuged plasma and serum samples were collected into fresh polypropylene tubes. Similar to Lo et al suggestion, Mattos-Arruda et al. provide for the teaching that circulating blood biomarkers promise to become non-invasive real-time surrogates for tumour tissue based biomarkers. Circulating biomarkers have been investigated as tools for breast cancer diagnosis, the dissection of breast cancer biology and its genetic and clinical heterogeneity, prognostication, prediction and monitoring of therapeutic response and resistance. Laktionov et al. provide further evidence and teaching that both DNA and RNA can be identified and analyzed for method to diagnose cancer. Laktionov et al. provide that in the blood there are two sources, a free from and one that is bound to blood cells, such as leukocytes which possess nucleic acid binding proteins at their surface.

In addition, Lo et al provide that future studies should investigate the temporal relation between gestation and the appearance and concentration of fetal DNA in maternal plasma. As well as sex-linked disorders, techniques for fetal-DNA detection in maternal plasma or serum can also be used to detect many paternally inherited DNA sequences that differ from their maternal counterparts. Clinical examples include fetal rhesus D status assessment and detection of certain haemoglobinopathies. The plasma or serum-based approach might also be applicable to screening for chromosomal aneuploidies (such as Down's syndrome) if there is a quantitative difference in the concentration of fetal DNA in maternal plasma and serum between affected and normal pregnancies; this is a situation analogous to the high concentration of fetal cells detectable in pregnancies that involve aneuploid fetuses. Laktionov et al provide the observation for different stages of cancer providing different amounts of nucleic acids being bound when analyzing different patients and different stage samples. Further, it is noted by Lo et al. and acknowledged that there are interesting similarities between a growing fetus and a neoplasm:

both are immunologically foreign and have an extensive vascular interface with their hosts, noting the results as analogous to that of Nawroz and colleagues, who detected in head and neck cancer patients mutant plasma DNA predominantly in those with high tumor load. Similar to Nawroz noted by Lo et al. at the time of filing, the presence of circulating cell-free DNA in humans was known as evidenced by Ellinger et al, Jung et al and Shaw et al. who provide detailed examples of how cell-free circulation DNA can be used to evaluate patients with cancer. Each Ellinger et al, Jung et al and Shaw et al. provide a detailed analysis to provide evidence that isolated cell free DNA can be used to identify genetic variants in cancer patients, both in quantity and in specific mutations associated with a given cancer and possible roles for treatment or care. Similar to Lo et al., Lewis discloses methods for separating cell-free DNA from a maternal blood sample (para [0010] "The present invention provides methods for enriching fetal nucleic acids from a maternal sample, such as, whole blood .... obtained from a pregnant female") and that analysis of fetal cell-free DNA offers one potential approach to non-invasive prenatal diagnosis" (para [0005] "Analysis of cell free fetal DNA (cffDNA) in maternal plasma offers one potential approach to non-invasive prenatal diagnosis"). Lewis further teaches that maternal cell-free DNA is also present in blood (para [0006] "cell free maternal DNA is also present in blood in quantitative excess"). Given that leukocytes are present in the buffy coat and serve as nucleated blood cells as provided in Lo et al. that can serve as a source of patient nucleic acid in a blood sample, one of ordinary skill in the art would have readily appreciated that nucleic acid extracted from maternal leukocytes can be compared to isolated cell free DNA in order to determine whether the cell free DNA is maternal or fetal cell free DNA, wherein fetal cell free DNA can be used to make a prenatal diagnosis of the growing fetus. Thus, one of ordinary skill in the art would have found it obvious to use the method of Lo et al to include a step of separating a

maternal blood sample into at least a first component that includes cell-free nucleic acid molecules and a second component that includes a cellular fraction comprising leukocytes which are known to be present in the buffy coat, as taught by both Lo et al and Lewis, in order to verify that cell-free nucleic acid is from the fetus, and to use the fetal cell-free nucleic acid to provide a non-invasive prenatal diagnosis of the fetus, as taught by Lo et al and Lewis. Finally, in view of the art as a whole, the use of genetic markers can be used to detect whether cancer exists within the patient as well as determine the origin of the cancer based on the specificity of the genetic marker being used. The skilled artisan would know that specific types of identified cancers would require different and unique types of treatments making obvious 'compositions' that would be used in the treatment of cancer.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph T Woitach whose telephone number is (571)272-0739. The examiner can normally be reached Mon-Fri; 9:00-5:00.

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, Karlheinz R Skowronek can be reached on 571 272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Joseph Woitach/
Primary Examiner, Art Unit 1631

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	**Art Unit**
	Joseph T Woitach	1631

CPC - Searched*		
Symbol	**Date**	**Examiner**

CPC Combination Sets - Searched*		
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* 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**
reviewed applications/patents in priority listing	02/17/2022	jw
PALM for inventor and assignee/applicant	02/17/2022	jw
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SEARCH	02/17/2022	jw
Google	04/04/2022	jw
SEARCH	04/04/2022	jw
PALM for related applications by inventor and Applicant/assignee	04/04/2022	jw
global portfolio	04/04/2022	jw

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/494,513	West, John
	Examiner	**Art Unit**
	Joseph T Woitach	1631

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

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Genomic analysis of circulating **cell-free DNA** infers breast **cancer** dormancy

JA Shaw, K Page, P Blighe, N Rava, D Guttery ... - Genome ..., 2012 - genome.cshlp.org

... Next, we compared SNP concordance between paired **leukocyte** and plasma **cfDNA** in all patients. The healthy controls had the highest mean concordance of SNP genotype calls (...

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Limitations and opportunities of technologies for the analysis of **cell-free DNA** in **cancer** diagnostics

P Song, LR Wu, YH Yan, JX Zhang, T Chu ... - Nature Biomedical ..., 2022 - nature.com

... limitations of **cfDNA** analysis for **cancer** diagnostics. **cfDNA** diagnostics in **cancer** care ... Thus, contamination of **cfDNA** with **leukocyte** genomic DNA will dilute the fraction of ...

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Circulating tumor cells versus tumor-derived **cell-free DNA**: rivals or partners in **cancer** care in the era of single-cell analysis?

E Kilgore, SS Jeffrey - Genome medicine, 2013 - genomemedicine.biomedcentral ...

... **cfDNA** can be derived from normal cells, including normal **leukocytes** that undergo apoptosis, and **cancer** ... , patients without **cancer**, patients with benign tumors, and **cancer** patients. ...

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Evaluation of TERT promoter mutations in urinary **cell-free DNA** and sediment DNA for detection of bladder **cancer**

S Stasik, F Sakoparnig, U Rebernig, M Fraedrich ... - Clinical ..., 2019 - Elsevier

... implications of **cfDNA** in urine for the detection of bladder **cancer** (BCa) is sparse. ... **leukocyte**-rich urines were higher in **cfDNA** than in sDNA, indicating a diagnostic advantage of ...

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Blood-based detection of colorectal **cancer** using **cancer**-specific DNA methylation markers

NY Cho, JW Park, X Wei, YJ Shin, JK Kang, SH Song ... - Diagnostics, 2020 - mdpi.com

... markers specific for **cell-free DNA** (**cfDNA**) from patients with colorectal **cancer** (CRC). By ... mucosal tissues or blood **leukocytes**, we identified eight **cancer**-specific methylated loci (...

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Urinary **cell-free DNA** as a potential tumor marker for bladder **cancer**

HW Chang, KH Tan, LC Shen ... - ... journal of biological ..., 2007 - journals.sagepub.com

... While **leukocytes** and bacteria could interfere with large-fragment ucf-DNA concentrations ... These results suggest that **leukocyte** DNA, if present, does not significantly interfere with the ...

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Distinct profile of **cell-free DNA** in malignant pleural effusion of non-small cell lung **cancer** and its impact on clinical genetic testing

Y Yu, J Qiao, L Shen, W Ji, S Lu - International journal of medical ..., 2021 - ncbi.nlm.nih.gov

... Damaged tumor cells together with apoptotic or pyroptotic **leukocytes** may release large amounts of **cfDNA** in the pleural space, making pleural fluid a possible rich source of ...

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Blood **leukocytes** methylation levels analysis indicate methylated plasma test is a promising tool for colorectal **cancer** early detection

Z Chen, G Zhao, K Wang, X Wang, Y Ma ... - ... of Cancer, 2021 - ncbi.nlm.nih.gov

... in **leukocyte** genomic DNA (gDNA) in individuals with or without **cancer** were also present in **cfDNA**, raising the possibility of false positive in detection of **cancer**-derived mutations 5 ...

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Cell-surface-bound circulating DNA in the blood: Biology and clinical application
S Yamkovoi, P Laktionov - IUBMB life, 2019 - Wiley Online Library
... **leukocytes**. Although less well characterized than **cell-free DNA** (**cfDNA**) in plasma and serum, **leukocyte** ... ; however, as with **cfDNA**, in patients with **cancer** a proportion is derived from ...
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Circulating **cell-free DNA** content as blood based biomarker in endometrial **cancer**
L Cocchiglia, G Cuomo, M De Angeli, S Mancini... - Oncotarget, 2017 - ncbi.nlm.nih.gov
... A recent molecular epidemiological study focused on evaluating the association between mtDNA copy number in peripheral blood **leukocytes** (PBLs), and EC risk demonstrated that low ...
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colorectal cancer **in peripheral blood**
peripheral blood metastatic breast cancer
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1631
PERSONALIS, INC.	Examiner: Joseph T. Woitach
Serial No.: 17/494,513	Customer No. 182685
Filed: October 5, 2021	Confirmation No. 8186
For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Attorney Docket No. 48929.4008/US03

Filed via EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTIONS

Commissioner:

This communication is responsive to the Non-final Office Action of February 28, 2022. Applicants submit this response on or before May 28, 2022, making it timely.

Amendments to the Claims begins on page 2 of this paper; and

Remarks begin on page 6 of this paper.

Certificate of EFS-Web Transmission

Date:

I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO.

/Sheila Gloss/
SHEILA GLOSS
4157-0837-4837.4

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listing of claims in the application.

1-9. (Canceled)

10. (Currently amended) A method of analyzing a biological sample obtained from a subject being screened for a disease, comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by independently sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, and wherein (i) said first set of nucleic acid molecules is extracted from a first component separated from a blood sample of said subject <u>from a non-fetal source</u>, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a second component separated from said blood sample <u>from a non-fetal source</u>;

(b) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants in said first set of sequence reads that is not present in said second set of sequence reads; [[and]]

(c) subsequent to (b), identifying one or more second mosaic variants in a second sample of said subject, wherein said second sample is obtained from a source or at a time point that is different than said blood sample[[.]]; <u>and</u>

<u>(d) providing a report based on an identification of said first mosaic variants or said second mosaic variants.</u>

11. (Previously presented) The method of claim 10, further comprising identifying one or more third mosaic variants in a third sample of said subject, which third sample is obtained from a source or at a time point that is different than said blood sample and said second sample.

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12. (Currently amended) The method of claim 10, further comprising providing ~~a report and/or~~ a recommendation for a therapeutic intervention based on an identification of said first mosaic variants or said second mosaic variants.

13. (Previously presented) The method of claim 10, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

14. (Previously presented) The method of claim 11, wherein said second or third sample comprises a blood sample, a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy, a saliva sample, a buccal swab, a urine sample, a semen sample, a cerebrospinal fluid sample, or a breast milk sample of said subject.

15. (Previously presented) The method of claim 11, wherein said one or more first, second, or third mosaic variants are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

16. (Previously presented) The method of claim 11, wherein said one or more first, second, or third mosaic variants are causal or predisposing for a disease.

17. (Previously presented) The method of claim 11, wherein said one or more first, second, or third mosaic variants are non-causal for a disease.

18. (Previously presented) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said blood sample, second sample, or third sample.

19. (Previously presented) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said blood sample and said second sample or said third sample.

20. (Currently amended) A method for early disease detection in a subject, said method comprising:

(a) obtaining a blood sample from said subject;

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(b) extracting (i) a first set of nucleic acid molecules from a first component separated from a blood sample of said subject from a non-fetal source and (ii) a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample from a non-fetal source;

(c) quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules present in said first component separated from a blood sample;

(d) comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity;

(e) if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads generated by independently sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules;

(f) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants in said first set of sequence reads that is not present in said second set of sequence reads; [[and]]

(g) subsequent to (f), identifying one or more second mosaic variants in a second sample of said subject, which second sample is obtained from a source or at a time point that is different than said blood sample[[.]]; and

(h) providing a report based on an identification of said first mosaic variants or said second mosaic variants.

21. (Previously presented) The method of claim 20, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

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22. (Previously presented) The method of claim 20, further comprising identifying one or more third mosaic variants in a third sample of said subject, which third sample is obtained from a source or at a time point that is different than said blood sample and said second sample.

23. (Previously presented) The method of claim 20, wherein said second or third sample comprises a blood sample, a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy, a saliva sample, a buccal swab, a urine sample, a semen sample, a cerebrospinal fluid sample or a breast milk sample of said subject.

24. (New) The method of claim 20, further comprising providing a recommendation for a therapeutic intervention based on an identification of said first mosaic variants or said second mosaic variants.

25. (New) The method of claim 20, wherein said one or more first, second, or third mosaic variants are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

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REMARKS

A. Status of the claims

Applicant initially notes that the Office has withdrawn the restriction requirement previously issued on 1-7-2022. Applicant herein has amended claim 10 and claim 20 to clarify that the claimed method provides a report based on an identification of one or more variants and that the variants are from a non-fetal source. Additionally, claim 12 has been amended. These amendments are fully supported throughout the specification, including at, for example, paragraphs [0016] and [0058] of the specification. Further, new claims 24 and 25 are added in this Amendment. New claims 24 and 25 are fully supported throughout the specification, including at, for example, paragraphs [0016] and [0040]. Accordingly, claims 10-25 are currently pending in this application. Applicant respectfully requests entry of the claims as amended.

B. Double Patenting

Claims 10-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of U.S. Patent No. 11,142,802 (Application No. 16/132123, allowed 8/9/2021).

Claims 10-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of U.S. Patent No. 10,125,399 (Application No. 14/929075, allowed 10/24/2018).

Claims 10-23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 10-17, 19-24, 27, and 29-33 of co-pending U.S. Application No. 17/065406 (RCE filed 1/28/2022).

For the purposes of expediting prosecution of the present application, Applicant files herewith a Terminal Disclaimer and respectfully submits that the Office's non-statutory double patenting rejection of claims 10-23 are moot and should be withdrawn.

C. Rejection under 35 U.S.C. § 101

The Office has rejected claims 10-23 under 35 U.S.C. §101, because the claimed invention is allegedly directed to a judicial exception without significantly more. Applicant

respectfully disagrees. Without conceding to the basis of the rejection, Applicant has amended claims 10 and 20 to clarify the claimed subject matter. Initially, Applicant makes note that the Office admits that the claims, "…are found to be **directed to a statutory category** of a process…" (Office Action dated 2-28-2022, p.10, emphasis added). Next, Applicant recognizes that under the guidance set forth in the "October 2019 Patent Eligibility Guidance Update" issued October 17, 2019, referred to herein as "2019 Guidance Update", the procedures under Step 2A for determining whether a patent claim is directed to a judicial exception have been revised.

Specifically, the 2019 Guidance Update states in relevant part that:

> "If the claim integrates the judicial exception into a practical application based upon evaluation of these considerations, the additional limitations impose a meaningful limit on the judicial exception, and the claim is eligible at Step 2A. For example, if the additional limitations reflect an improvement in the functioning of a computer, or an improvement to another technology or technical field, the claim integrates the judicial exception into a practical application and thus imposes a meaningful limit on the judicial exception, claims of the instant application are directed to an improvement to other technology or technological field. **No further analysis is required. The claim is eligible at Step 2A**" (p. 11; emphasis added)

For example, in *McRO, Inc. dba Plant Blue v. Bandai Namco Games America, Inc.* 837 F.3d 1299, the Federal Circuit held that the claimed methods of automatic lip synchronization and expression animation using computer-implemented rules were patent eligible under § 101. As set forth in MPEP 2106.05(a)(II), the basis for the *McRO* court's decision was that the claims were directed to an improvement in computer animation and thus did not recite a concept similar to previously identified abstract idea. The *McRO* court indicated that it was the incorporation of the particular claimed rules in computer animation that "improved [the] existing technological process", unlike cases such as *Alice* where a computer was merely used as a tool to perform an existing process. MPEP 2106.05(a)(II) The *McRO* court also noted that the claims at issue described a specific way (use of particular rules to set morph weights and transitions through phonemes) to solve the problem of producing accurate and realistic lip synchronization and

facial expressions in animated characters, rather than merely claiming the idea of a solution or outcome, and thus were not directed to an abstract idea. *Id.*

Step 2A Prong One – The method of claims 10 and 20 do not "recite an abstract idea, law of nature, or natural phenomenon".

As in *McRO*, the method of claim 10 applies rules to analyze a biological sample obtained from a subject being screened for a disease and generate a report identifying said health condition or diseased. Claim 10 recites, "…**obtaining a first set of sequence reads and a second set of sequence reads**…**wherein** (i) **said first set of nucleic acid molecules is extracted from a first component separated from a blood sample of said subject from a non-fetal source**, and (ii) **said second set of nucleic acid molecules is extracted from leukocytes from a second component separated from said blood sample from a non-fetal source**…**using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants** in said first set of sequence reads that is not present in said second set of sequence reads…and (d) **providing a report based on an identification of said first mosaic variants or said second mosaic variants**." This claim recites tangible elements and nowhere recites a judicial exception.

Further, as in *McRO*, the method of claim 20 applies rules for early disease detection in a subject and generate a report identifying said health condition or diseased. Claim 20 recites, "…**obtaining a blood sample**…**extracting** (i) **a first set of nucleic acid molecules from a first component separated from a blood sample of said subject from a non-fetal source** and (ii) **a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample from a non-fetal source**…**quantitating**…**to determine an amount of nucleic acid molecules**…**obtaining a first set of sequence reads and a second set of sequence reads** generated by independently sequencing nucleic acid molecules…**using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants**…and (h) **providing a report based on an identification of said first mosaic variants or said second mosaic variants**." This claim recites tangible elements and nowhere recites a judicial exception.

Accordingly, Applicant submits that independent claims 10 and 20 and dependent claims thereof should be found to be subject matter eligible at Step 2A Prong One.

Step 2A Prong Two – The method of claims 10 and 20 recite "additional elements that integrate" the alleged judicial exception "into a practical application".

Applicant respectfully submits that, although the claims should be found patent eligible under Step 2A Prong One, claim 10 and claim 21 also satisfy Step 2A Prong Two because the claims recite additional elements that integrate the alleged judicial exception into a practical application. As explained in the 2019 Guidance Update, "…the evaluation of Prong Two requires the use of considerations (e.g. improving technology…) identified by the Supreme Court and the Federal Circuit to ensure that the claim as a whole "integrates [the] judicial exception into a practical application [that] will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception…"" (2019 Guidance Update, p.11, second paragraph). As noted above, the 2019 Guidance Update further states, "…if the additional limitations reflect an improvement in the functioning of a computer, or an improvement to another technology or technical field, the claim integrates the judicial exception into a practical application and thus imposes a meaningful limit on the judicial exception." (2019 Guidance Update, p.11, final paragraph).

The Application discloses techniques, similar to the rules of *McRO*, for "analyzing a biological sample obtained from a subject being screened for a disease" (claim 10) and "early disease detection in a subject" (claim 20) using sequence information from different components of a blood sample from a subject from a non-fetal source. For instance, the instant application discloses:

> "The method may also be useful to perform tumor vs normal analysis without a tissue specimen from the tumor, and thus can be used to identify specific variants in the tumor and to recommend specific anti-cancer drugs based on the mutation to be targeted. The normal analysis may be performed on white blood cells (i.e., leukocytes) prior to the development of the tumor. In some cases, **the normal analysis and the tumor analysis are performed on a single blood sample**. In this case, whole blood can be collected and centrifuged to separate the plasma which contains the cfDNA, the buffy coat which

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contains the white blood cells, and the red blood cells. Nucleic acids can be extracted from the plasma and the white blood cells and sequenced. In some cases, the cfDNA may contain distal nucleic acids that originated from a tumor. **In these cases, tumor variants may be identified by identifying mosaic variants in the cfDNA that are not represented in the white blood cells ('normal'). In some cases, the tumor variants are causal variants (i.e., tumor-causing).**" (Application, paragraph [0058], emphasis added).

The methods of claim 10 and claim 20 present improvements in a technical field (e.g., cancer diagnostics otherwise requiring biopsy) at least because the methods yield at least improved detection of a tumor or cancer without invasive sampling. As in *McRO*, the identification of one or more variants from a blood sample can obviate the need to manually obtain an additional tumor biopsy or cancer sample from a subject. Rather, a single blood sample may be analyzed. *See* Application, paragraph [0054] (above) and Example 4. In view of the foregoing, applicant respectfully submits the methods of claim 10 and claim 20 integrates any alleged judicial exception into at least the aforementioned practical application(s) and thus imposes meaningful limit(s) on the alleged judicial exception.

Accordingly, Applicant submits that independent claims 10 and 20 and dependent claims thereof should further be found to be subject matter eligible at Step 2A Prong Two.

Step 2B – The method of claims 10 and 20 recite additional elements that amount to "significantly more" than any alleged judicial exception.

Applicant respectfully submits that, although the claims should be found patent eligible under Step 2A Prong One and/or Step 2A Prong Two, claim 10 and claim 20 also satisfies Step 2B because the claims include elements that are not well-understood, routine, or conventional. For example, it is not routine or conventional to "…**obtaining a first set of sequence reads and a second set of sequence reads** by independently sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules…**wherein** (i) **said first set of nucleic acid molecules is extracted from a first component separated from a blood sample of said subject from a non-fetal source**, and (ii) **said second set of nucleic acid molecules is extracted from a second component separated from said blood**

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sample from a non-fetal source...and (d) **providing a report based on an identification of said first mosaic variants or said second mosaics variants**." as recited in claim 10. Further, it is not routine or conventional to "...obtaining a blood sample...**extracting** (i) **a first set of nucleic acid molecules from a first component separated from a blood sample of said subject from a non-fetal source** and (ii) **a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample from a non-fetal source**...**quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules**...**comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity**...**if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads** generated by independently sequencing nucleic acid molecules...**using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants**...and (h) **providing a report based on an identification of said first mosaic variants or said second mosaic variants**." as recited in claim 20.

Accordingly, Applicant submits that independent claims 10 and 20 and dependent claims thereof should further be found to be subject matter eligible at Step 2B.

In summation, at every step of the *Alice/Mayo* framework and the revised analysis provided in the 2019 Guidance Update, the claims should be found to be subject matter eligible. For Step 1 of the analysis, the Office admits that the claims, "...are found to be directed to a statutory category of a process..." (Office Action dated 2-28-2022, p.10). For Step 2 of the analysis, the claims: (1) do not "recite" a judicial exception (Step 2A Prong One), (2) are not "directed to" a judicial exception (Step 2A Prong Two), and (3) recite "significantly more" than any alleged judicial exception (Step 2B). Accordingly, Applicant respectfully submits that the 35 U.S.C. § 101 rejections of independent claims 10 and 20 and dependent claims 11-19 and 21-23 be withdrawn.

D. Rejection under 35 U.S.C. § 103

The Office has rejected claims 10-23 under 35 U.S.C. 103 as allegedly being unpatentable over Lo et al. (1997) ("Lo"), De Mattos-Arruda et al. (2013) ("De Mattos-Arruda"), Laktionov et al. (2004) ("Laktionov"), Ellinger et al (Urologic Oncology 29:124-129 (2011)) ("Ellinger"), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)) ("Jung"), Shaw et al. (Genome Research 22:220-231 (2012)) ("Shaw"), Lewis et al. (US 2012/0058480 Al) ("Lewis"), and Green et al. (US 2005/0260645 Al) ("Green").

Without conceding to the basis of the rejection, and solely to expedite prosecution of this application, Applicant has amended claim 10 to clarify that the claimed method of analyzing a biological sample obtained from a subject being screened for a disease identifies one or more mosaic variants using a first set of nucleic acid molecules extracted from a first component separated from a blood sample from a non-fetal source and a second set of nucleic acid molecules extracted from leukocytes from a second component separated from a blood sample from a non-fetal source, and further provides a report based on the identification of such variants. Applicant submits that the claims as amended are not obvious over the asserted combination of Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green because none of the references, alone or in combination, teaches or discloses all of the elements of this claim.

For example, nothing in Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, or Green teaches or discloses, or even suggests, "A method of analyzing a biological sample obtained from a subject being screened for a disease…wherein (i) said **first set of nucleic acid molecules is extracted from a first component separated from a blood sample of said subject from a non-fetal source**, and (ii) said **second set of nucleic acid molecules is extracted from leukocytes from a second component separated from said blood sample from a non-fetal source**…and (d) **providing a report based on an identification of said first mosaic variants or said second mosaic variants**", as recited in claim 10. Since none of the references individually disclose these elements of the claimed invention, the combined teaching of these references necessarily fail to render the present claim obvious.

Further, without conceding to the basis of the rejection, and solely to expedite prosecution of this application, Applicant has amended claim 20 to clarify that the claimed

method for early disease detection in a subject identifies one or more mosaic variants using a first set of nucleic acid molecules extracted from a first component separated from a blood sample from a non-fetal source and a second set of nucleic acid molecules extracted from leukocytes from a second component separated from a blood sample from a non-fetal source, and further provides a report based on the identification of such variants. Applicant submits that the claims as amended are not obvious over the asserted combination of Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green because none of the references, alone or in combination, teaches or discloses all of the elements of this claim.

For example, nothing in Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, or Green teaches or discloses, or even suggests, "A method for early disease detection in a subject…(b) extracting (i) **a first set of nucleic acid molecules from a first component separated from a blood sample of said subject from a non-fetal source** and (ii) **a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample from a non-fetal source**…and (h) **providing a report based on an identification of said first mosaic variants or said second mosaic variants**", as recited in claim 20. Since none of the references individually disclose these elements of the claimed invention, the combined teaching of these references necessarily fail to render the present claim obvious.

Claims 11-19 depend from and include all of the elements of claim 10 and recite additional elements of particular advantage and utility. Claims 21-23 depend from and include all of the elements of claim 20 and recite additional elements of particular advantage and utility. As such, the asserted combination of Lo, De Mattos-Arruda, Laktionov, Ellinger, Jung, Shaw, Lewis, and Green also fails to render the present claims obvious.

In view of the foregoing, Applicant submits that claims 10-23, as amended herewith, are in compliance with 35 U.S.C. § 103. As such, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

E. Conclusion

For at least the reasons set forth above, it is submitted that claims 10-25 are in condition for allowance. A Notice of Allowance is earnestly solicited.

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If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

The Applicants reserve the right to pursue at a later date any previously pending or other claims that capture any subject matter supported by the present disclosure. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have disclaimed or disavowal any subject matter supported by the present application.

Except for issues fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees including fees due under 37 CFR § 1.16 and 1.17, which may be required, and including any required extension of time fees, or credit any overpayment to Deposit Account 15-0665 (Docket Reference: 48929.4008/US03).

Respectfully submitted,

Orrick, Herrington & Sutcliffe LLP

Dated: 3/29/2022

By: /Alex Straughn/
Alex Straughn, Reg. No. 80,155, for
Gargi Talukder, Reg. No. 61,368

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Telephone: (949) 567-6700
Facsimile: (949) 567-6710

Electronic Acknowledgement Receipt

EFS ID:	45341425
Application Number:	17494513
International Application Number:	
Confirmation Number:	8186
Title of Invention:	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN
First Named Inventor/Applicant Name:	John West
Customer Number:	182685
Filer:	Alex Ryan Straughn/Sheila Gloss
Filer Authorized By:	Alex Ryan Straughn
Attorney Docket Number:	48929.4008/US03
Receipt Date:	29-MAR-2022
Filing Date:	05-OCT-2021
Time Stamp:	12:31:44
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		48929_4008_US03_NFOAResponse.pdf	186066 364157fca43087aa0015f81d549ce26d81a020dc	yes	14

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Request for Reconsideration-After Non-Final Rejection	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	14
Warnings:			
Information:			
	Total Files Size (in bytes):	186066	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Doc Code: 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	17494513
Filing Date	05-Oct-2021
First Named Inventor	John West
Attorney Docket Number	48929.4008/US03
Title of Invention	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

☒ 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
Personalis, 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)

17065406 filed on 10/07/2020

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)

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10125399

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 80155

○ 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	/Alex Straughn/
Name	Alex Straughn

*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:	17494513
Filing Date:	05-Oct-2021
Title of Invention:	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN
First Named Inventor/Applicant Name:	John West
Filer:	Alex Ryan Straughn/Sheila Gloss
Attorney Docket Number:	48929.4008/US03

Filed as Small 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	2814	1	170	170
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**170**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 17494513

Filing Date: 05-Oct-2021

Applicant/Patent under Reexamination: West

Electronic Terminal Disclaimer filed on March 29, 2022

☒ 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:	45341327
Application Number:	17494513
International Application Number:	
Confirmation Number:	8186
Title of Invention:	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN
First Named Inventor/Applicant Name:	John West
Customer Number:	182685
Filer:	Alex Ryan Straughn/Sheila Gloss
Filer Authorized By:	Alex Ryan Straughn
Attorney Docket Number:	48929.4008/US03
Receipt Date:	29-MAR-2022
Filing Date:	05-OCT-2021
Time Stamp:	12:30:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$170
RAM confirmation Number	E20223SC30210575
Deposit Account	150665
Authorized User	Sheila Gloss

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

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	46389 2ca04e6322a567ef91d5b6d620cc1ff8eebeb139	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	38019 46f04fd6bfa949f5fc7f9938e6dd9cec201169dc	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	84408		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

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ORRICK, HERRINGTON & SUTCLIFFE LLP
(Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

Courtesy Reminder for
Application Serial No: 17/494,513

Attorney Docket No: 48929.4008/US03
Customer Number: 182685
Date of Electronic Notification: 02/28/2022

This is a courtesy reminder that new correspondence is available for this application. If you have not done so already, please review the correspondence. The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

An email notification regarding the correspondence was sent to the following email address(es) associated with your customer number:
ipprosecution@orrick.com
vsantos@orrick.com

To view your correspondence online or update your email addresses, please visit us anytime at **https://ppair-my.uspto.gov/pair/PrivatePair.**
If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov or call 1-866-217-9197.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 02/28/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
02/28/2022	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
vsantos@orrick.com

Office Action Summary	Application No. 17/494,513	Applicant(s) West, John	
	Examiner Joseph T Woitach	Art Unit 1631	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 2/9/2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 11-23 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) 11-23 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 10/5/2021 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

TrackOne Request

Applicants request filed 10/5/2021 has been granted (see paper mailed 12/8/2021).

Applicant's response filed 2/9/2022 to the Restriction requirement mailed 1/7/2022 did not require an extension of time.

Applicant's Amendment

Applicant's preliminary amendment filed 2/9/2022 has been received and entered. Claims 1-9 were previously cancelled, and claims 11-23 appear to have no editor marks and have only updated status identifiers.

Claims 11-23 are pending.

Election/Restriction

Applicant's election without traverse of Group II, and the species of a blood sample and SNPs in the reply filed on 2/9/2022 is acknowledged.

Upon initial search and review of the specification it does not appear to be a burden to examine both groups as Group I appears to comprise similar but broader steps that are required of the elected method for screening a patient for a disease. Further, upon review of the elected species of blood as a sample source, it appears that using controls or sample sources for further analysis are known and obvious based on the disease being analyzed; and similarly the type of

genetic variant being analyzed/observed would also be known or associated with the disease being analyzed. Accordingly, the restriction requirement **is withdrawn.**

Claims 10-23 are pending and currently under examination as drawn to a method of analyzing a biological sample by comparing sequence reads obtained from a blood component and the comparison to samples taken at a different time from the first for patient screening are currently under examination.

Priority

This application filed 10/5/2021 is a Divisional of 16/132123, now US Patent 11142802, which is a continuation of 14/929075, now US Patent 10125399, which claims benefit to US provisional application 2/072936 filed 10/30/2014; and is related to 17/065406 filed 10/7/2020 through parent 16/132123, and to PCT/US15/58483 filed 10/30/2015.

Information Disclosure Statement

The two information disclosure statements (IDS) submitted on 10/5/2021 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where

the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 10-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of U.S. Patent No. 11142802 (16/132123 allowed 8/9/2021). Although the claims at issue are not identical, they are not patentably distinct from each other because each comprise steps that require extraction of two sources of DNA, cfDNA and DNA that is not cfDNA, from blood, and analysis of the read data from the sources over time for broadly analyzing or screening a subject for any genetic variant associated with any disease. In both, the dependent claims provide for further detail in regarding sample source or how the DNA is analyzed and possible types of variants that might be detected. A copy of the independent claims are provided below for comparison.

Claim 10 of the instant application:

A method of analyzing a biological sample obtained from a subject being screened for a disease, comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by independently sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, and wherein

(i) said first set of nucleic acid molecules is extracted from a first component separated from a blood sample of said subject, and

(ii) said second set of nucleic acid molecules is extracted from leukocytes from a second component separated from said blood sample;

(b) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants in said first set of sequence reads that is not present in said second set of sequence reads; and

(c) subsequent to (b), identifying one or more second mosaic variants in a second sample of said subject, wherein said second sample is obtained from a source or at a time point that is different than said blood sample.

Independent claim of '802:

A method for identifying at least one mosaic variant of a subject, comprising:

(a) extracting

(i) a first set of nucleic acid molecules from a cell-free portion of a blood sample of said subject and

(ii) a second set of nucleic acid molecules from leukocytes in said blood sample of said subject;

(b) independently sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules to obtain at least a first set of sequence reads and a second set of sequence reads, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules; and

(c) using at least said first set of sequence reads and said second set of sequence reads to identify said at least one mosaic variant

(1) in said first set of sequence reads that is not present in said second set of sequence reads or

(2) in said second set of sequence reads that is not present in said first set of sequence reads.

Dependent claim:

The method of claim 1, further comprising performing an assay that is specific to said at least one mosaic variant of said subject at a subsequent time point.

Claims 10-23 are rejected on the ground of nonstatutory double patenting as being unpatentable over the claims of U.S. Patent No. 10125399 (14/929075 allowed 10/24/2018). Although the claims at issue are not identical, they are not patentably distinct from each other because each comprise steps that require extraction of two sources of DNA, cfDNA and DNA that is not cfDNA, from blood, and analysis of the read data from the sources over time for broadly analyzing or screening a subject for any genetic variant associated with any disease. In both, the dependent claims provide for further detail in regarding sample source or how the DNA is analyzed and possible types of variants that might be detected. A copy of the independent claims are provided below for comparison.

Independent claim of '399:

A method for identifying a non-fetal source of cell-free or surface-bound nucleic acid molecules in a blood sample from a body of a subject, comprising:

(a) separating said blood sample into at least a first component that includes said cell- free or surface-bound nucleic acid molecules and a second component that includes leukocytes, wherein said non-fetal source of said cell-free or surface-bound nucleic acid molecules is unknown;
(b) extracting nucleic acid molecules from said first component and said leukocytes from said second component;
(c) independently sequencing extracted nucleic acid molecules from said first component and second component to generate a first set of sequence reads and a second set of sequence reads from said first and second components, respectively; and
(d) subsequent to (c), identifying said non-fetal source of said cell-free or surface-bound nucleic acid molecules in said body of said subject.

Claims 10-23 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 10-17, 1924, 27, 29-33 of copending Application No. 17/065406 (RCE filed 1/28/2022). Although the claims at issue are not identical, they are not patentably distinct from each other because each comprise steps that require extraction of two sources of DNA, cfDNA and DNA that is not cfDNA, from blood, and analysis of the read data from the sources over time for broadly analyzing or screening a subject for any genetic variant associated with any disease. In both, the dependent claims provide for further detail in regarding sample source or how the DNA is analyzed and possible types of variants that might be detected. A copy of the independent claims are provided below for comparison.

Independent claim of '406:

A method for identifying one or more variants from a non-fetal source in a blood sample from a subject, comprising:

(a) from said blood sample from said subject comprising

(i) a plasma fraction comprising cell-free nucleic acid molecules and

(ii) a buffy coat fraction, obtaining nucleic acid molecules from said plasma fraction and said tissue sample buffy coat fraction, wherein said nucleic acid molecules comprise at least a subset of said cell-free nucleic acid molecules of said plasma fraction and at least a subset of nucleic acid molecules of said buffy coat fraction;

(b) assaying said nucleic acid molecules from said plasma fraction and said buffy coat fraction to generate sequence information comprising sequences derived from said at least a

subset of cell-free nucleic acid molecules and sequences derived from said at least said subset of nucleic acid molecules of said buffy coat fraction;

(c) subsequent to (b), identifying said one or more variants in said sequences derived from said cell-free nucleic acid molecules, wherein said sequences derived from said nucleic acid molecules of said buffy coat fraction are a normal; and

(d) providing a report and/or a therapeutic intervention based on an identification of said one or more variants.

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

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10-23 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter because the claimed invention is not directed to patent eligible subject matter. Based upon an analysis with respect to the claim as a whole, claims 10-31 do not recite something significantly different than a judicial exception. The rationale for this determination is explained below.

Claim analysis

Independent claim 10 is directed generally towards a method of detecting variants in circulating cell free DNA as compared to a reference tissue of a patient. The claim sets forth the steps of obtaining plasma and tissue samples, extracting nucleic acids from the samples, sequencing the nucleic acids that are present, and comparing the sequence data identifying possible variants that may be present between the two where the cfDNA is to be designated

'normal' in the analysis. Dependent claims set forth the types of variations that might be detected, such as copy number, SNPs, MNPs, inDels,.. or that the variant is associated with disease and/or possible treatment and that the method steps can be performed more than once at different time points for comparison of the variants at different times.

For step 1 of the 101 analysis, the claims are found to be directed to a statutory category of a process because the step of 'obtaining' requires a physical step to create the read data and thus is found to be directed to a statutory category of a method of analyzing nucleic acids in a sample.

For step 2A of the 101 analysis, the judicial exception of the claims are the steps of accessing and analyzing sequence data for differences/variants. The step of aligning and comparing sequence to arrive at the identification of variations between sequences are considered instructional steps. In view of the specification, the claim requires analyzing homology or computing similarity scores to determine differences in the sequences. The judicial exception is a set of instructions for analysis of sequence data, and appears to fall into the category of Mental Processes that is concepts performed in the human mind (including an observation, evaluation, judgment, opinion). Here, the claims do not require a computer, or any large amount or complexity of read sequence data, and could be performed on paper and the analysis could be performed in one's mind by comparing two sequences to see if there is any variant base between the two.

Recent guidance from the office requires that the judicial exception be evaluated under a second prong to determine whether the judicial exception is practically applied. In the instant case, the claims have an additional element of 'obtaining' which requires a physical step to create the read data. This judicial exception requires steps recited at high level of generality and

is not found to be a practical application of the judicial exception as broadly set forth, and provides for known combination of steps used in obtaining sequence read data (see also present specification for generalized listing of possible methods that can be use in the context of the steps). When the steps are viewed as physical steps or additional elements, it appears that the steps of obtaining sequence data/information and subsequently analyzing read data are separate from one another, and do not integrate back into the steps comprising additional elements. In this analysis, it appears that the step of obtaining sequence information is not integrated with the judicial exception, nor do the claims provide a practical application of the broad steps used to obtain sequence reads as a consequence of the analysis (as is the fact pattern in *Vanda*).

For Step 2B of the two step analysis, one is to determine whether any element or combination of elements, in the claim is sufficient to ensure that the claim as a whole amounts to significantly more than the judicial exception. In review of the evidence of record and given the breadth of the claims, there does not appear to be additional steps that are recited in the instantly claimed invention that would amount to significantly more than obtaining read data for analysis within the judicial exception. In this case the judicial exception is the information of where a given read aligns with a normal or reference sequence to potentially identify variations between reads. More specifically, it is noted that at the time of filing that using circulating cell free DNA was known and used for diagnostic methods and used for cancer intervention (see for example the teachings of Lo et al., De Mattos-Arruda et al. and Laktionov et al.) and are considered as known and conventional steps of obtaining and separating nucleic acids in a sample and obtaining genetic information about a patient. As such, the instant claims are drawn only to an abstract process that only manipulates genetic data and the judicial exception of a natural phenomenon (identification of variant sequences in circulating cell free DNA versus a tissue),

and are not directed to statutory subject matter. Dependent claims that set forth the use of an array or bead to capture specific sequences or the use of amplification to provide greater copy number for sequence analysis for analysis in the judicial exception, do not appear to be novel and appear to be a conventional means for 'enriching' or 'capturing' a sequence of interest (claims 20-24) from a sample as a step of isolation or purification consistent with the disclosure of the present specification. Therefore the result of the analysis is that the claims are directed towards a judicial exception, i.e. an abstract idea. In the instant case, the claims are directed to only the analysis and manipulation of data.

Without additional limitations, a process that employs mathematical algorithms or general considerations to manipulate existing information (in this case defining the presence/absence of variants/alleles in a mixed sample) to generate additional information (in this case describing the nucleic acids present in a sample) is not patent eligible. Furthermore, if a claim is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is non-statutory. In other words, patenting abstract ideas cannot be circumvented by attempting to limit the use [the idea] to a particular technological environment. For the instant claims, it is noted that a computer and/or program/product can be used to compare sequence reads for homology or variation (specification provides guidance for available tools), but this amount to mere instruction to implement an abstract idea in a computer environment. The hardware contemplated in the specification for the analysis do not offer a meaningful limitation beyond generally linking "the use of the method to a particular technological environment,' that is, implementation via computers." see Alice Corp v. CLS Bank Int'l 573 U.S. (2014). For the reasons set forth above, the claims are not

considered to recite something significantly different than a judicial exception and thereby are not directed to patent eligible subject matter.

One way to overcome a rejection for non-patent-eligible subject matter is to persuasively argue that the claimed subject matter is not directed to a judicial exception. Another way for the applicants to overcome the rejection is to persuasively argue that the claims contain elements in addition to the judicial exception that either individually or as an ordered combination are not well understood, routine, or conventional. Another way for the applicants to overcome the rejection is to persuasively argue that the claims as a whole result in an improvement to a technology. Persuasive evidence for an improvement to a technology could be a comparison of results of the claimed subject matter with results of the prior art, or arguments based on scientific reasoning that the claimed subject matter inherently results an improvement over the prior art. The applicants should show why the claims require the improvement in all embodiments.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

Claims 10-23 are rejected under 35 U.S.C. 103 as being unpatentable over Lo et al. (1997), De Mattos-Arruda et al. (2013), Laktionov et al. (2004), Ellinger et al (Urologic Oncology 29:124-129 (2001)), Jung et al (Clinica Chimica Acta 411:1611-1624 (2010)), Shaw et al (Genome Research 22:220-231 (2012)), Lewis et al. (US 2012/0058480 A1) and Green et al. (US 2005/0260645 A1).

Lo et al provide a report for the presence of cfDNA in maternal plasma and serum, and note that the presence of tumor DNA has been found and analyzed in cancer patients. The methods disclosed by Lo et al. used a rapid-boiling method to extract DNA from plasma and serum. DNA from plasma, serum, and nucleated blood cells from 43 pregnant women underwent a sensitive Y-PCR assay to detect circulating male fetal DNA from women bearing male fetuses. More specifically, maternal human blood samples were processed 1–3 h after venesection. Blood samples were centrifuged at 3000 *g*, and plasma and serum were carefully removed from the nucleic-acid-containing and plain tubes, respectively, and transferred into plain polypropylene tubes. Great care was taken to ensure that the buffy coat or the blood clot was undisturbed when plasma or serum samples, respectively, were removed. After removal of the

plasma samples, the red-cell pellet and buffy coat were saved for DNA extraction with a Nucleon DNA extraction kit. The plasma and serum samples then underwent a second centrifugation at 3000 *g*, and the re-centrifuged plasma and serum samples were collected into fresh polypropylene tubes. Similar to Lo et al suggestion, Mattos-Arruda et al. provide for the teaching that circulating blood biomarkers promise to become non-invasive real-time surrogates for tumour tissue based biomarkers. Circulating biomarkers have been investigated as tools for breast cancer diagnosis, the dissection of breast cancer biology and its genetic and clinical heterogeneity, prognostication, prediction and monitoring of therapeutic response and resistance. Laktionov et al. provide further evidence and teaching that both DNA and RNA can be identified and analyzed for method to diagnose cancer. Laktionov et al. provide that in the blood there are two sources, a free from and one that is bound to blood cells, such as leukocytes which possess nucleic acid binding proteins at their surface.

In addition, Lo et al provide that future studies should investigate the temporal relation between gestation and the appearance and concentration of fetal DNA in maternal plasma. As well as sex-linked disorders, techniques for fetal-DNA detection in maternal plasma or serum can also be used to detect many paternally inherited DNA sequences that differ from their maternal counterparts. Clinical examples include fetal rhesus D status assessment and detection of certain haemoglobinopathies. The plasma or serum-based approach might also be applicable to screening for chromosomal aneuploidies (such as Down's syndrome) if there is a quantitative difference in the concentration of fetal DNA in maternal plasma and serum between affected and normal pregnancies; this is a situation analogous to the high concentration of fetal cells detectable in pregnancies that involve aneuploid fetuses. Laktionov et al provide the observation for different stages of cancer providing different amounts of nucleic acids being bound when

analyzing different patients and different stage samples. Further, it is noted by Lo et al. and acknowledged that there are interesting similarities between a growing fetus and a neoplasm: both are immunologically foreign and have an extensive vascular interface with their hosts, noting the results as analogous to that of Nawroz and colleagues, who detected in head and neck cancer patients mutant plasma DNA predominantly in those with high tumor load. Similar to Nawroz noted by Lo et al. at the time of filing, the presence of circulating cell-free DNA in humans was known as evidenced by Ellinger et al, Jung et al and Shaw et al. who provide detailed examples of how cell-free circulation DNA can be used to evaluate patients with cancer. Each Ellinger et al, Jung et al and Shaw et al. provide a detailed analysis to provide evidence that isolated cell free DNA can be used to identify genetic variants in cancer patients, both in quantity and in specific mutations associated with a given cancer and possible roles for treatment or care. Similar to Lo et al., Lewis discloses methods for separating cell-free DNA from a maternal blood sample (para [0010] "The present invention provides methods for enriching fetal nucleic acids from a maternal sample, such as, whole blood .... obtained from a pregnant female") and that analysis of fetal cell-free DNA offers one potential approach to non-invasive prenatal diagnosis" (para [0005] "Analysis of cell free fetal DNA (cffDNA) in maternal plasma offers one potential approach to non-invasive prenatal diagnosis"). Lewis further teaches that maternal cell-free DNA is also present in blood (para [0006] "cell free maternal DNA is also present in blood in quantitative excess"). Given that leukocytes are present in the buffy coat and serve as nucleated blood cells as provided in Lo et al. that can serve as a source of patient nucleic acid in a blood sample, one of ordinary skill in the art would have readily appreciated that nucleic acid extracted from maternal leukocytes can be compared to isolated cell free DNA in order to determine whether the cell free DNA is maternal or fetal cell free DNA, wherein fetal cell free DNA can be

used to make a prenatal diagnosis of the growing fetus. Thus, one of ordinary skill in the art would have found it obvious to use the method of Lo et al to include a step of separating a maternal blood sample into at least a first component that includes cell-free nucleic acid molecules and a second component that includes a cellular fraction comprising leukocytes which are known to be present in the buffy coat, as taught by both Lo et al and Lewis, in order to verify that cell-free nucleic acid is from the fetus, and to use the fetal cell-free nucleic acid to provide a non-invasive prenatal diagnosis of the fetus, as taught by Lo et al and Lewis. Finally, in view of the art as a whole, the use of genetic markers can be used to detect whether cancer exists within the patient as well as determine the origin of the cancer based on the specificity of the genetic marker being used. The skilled artisan would know that specific types of identified cancers would require different and unique types of treatments making obvious 'compositions' that would be used in the treatment of cancer.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph T Woitach whose telephone number is (571)272-0739. The examiner can normally be reached Mon-Fri; 9:00-5:00.

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, Karlheinz R Skowronek can be reached on 571 272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Joseph Woitach/
Primary Examiner, Art Unit 1631

Notice of References Cited	Application/Control No. 17/494,513	Applicant(s)/Patent Under Reexamination West, John	
	Examiner Joseph T Woitach	Art Unit 1631	Page 1 of 1

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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
	17/494,513	West, John
	Examiner	**Art Unit**
	Joseph T Woitach	1631

CPC - Searched*		
Symbol	**Date**	**Examiner**

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

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

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Search Notes		
Search Notes	**Date**	**Examiner**
reviewed applications/patents in priority listing	02/17/2022	jw
PALM for inventor and assignee/applicant	02/17/2022	jw
Google	02/17/2022	jw
SEARCH	02/17/2022	jw

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

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Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2021-10-05
First Named Inventor	John West
Art Unit	
Examiner Name	
Attorney Docket Number	48929.4008US03

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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.

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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	/Gargi Talukder/	Date (YYYY-MM-DD)	2021-10-05
Name/Print	Gargi Talukder	Registration Number	61,368

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	2	9128861		2015-09-08	Gabor T. Bartha, et al.	
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Examiner Signature	/Joseph Woitach/	Date Considered	02/14/2022

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /JW/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2021-10-05
First Named Inventor	John West
Art Unit	
Examiner Name	
Attorney Docket Number	48929.4008US03

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	/Gargi Talukder/	Date (YYYY-MM-DD)	2021-10-05
Name/Print	Gargi Talukder	Registration Number	61,368

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.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /JW/

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Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

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Foresight v Personalis
IPR2024-00170

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	88,648	(blood and leukocyte and (separate or separated) and nucleic)".clm" "woitach.xp"	US-PGPUB; USPAT; USOCR; EPO	OR	ON	2022/02/14 10:50
L2	80,955	(blood and leukocyte and (separate or separated) and nucleic)".clm" and "woitach.xp"	US-PGPUB; USPAT; USOCR; EPO	OR	ON	2022/02/14 10:51
L3	80,955	(blood and leukocyte and (separate or separated) and nucleic)".clm" and "woitach.xp"	US-PGPUB; USPAT; USOCR; EPO	OR	ON	2022/02/14 10:51
L4	1	(blood and leukocyte and (separate or separated) and nucleic).clm. and woitach.xp.	US-PGPUB; USPAT; USOCR; EPO	OR	ON	2022/02/14 10:53

2/14/2022 10:57:58 AM

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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
17/494,513	10/05/2021	John West	48929.4008/US03

CONFIRMATION NO. 8186

182685
ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

PUBLICATION NOTICE

OC000000132043365

Title:METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Publication No.US-2022-0056538-A1
Publication Date:02/24/2022

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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Electronic Acknowledgement Receipt

EFS ID:	44955368
Application Number:	17494513
International Application Number:	
Confirmation Number:	8186
Title of Invention:	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN
First Named Inventor/Applicant Name:	John West
Customer Number:	182685
Filer:	Alex Ryan Straughn/Sheila Gloss
Filer Authorized By:	Alex Ryan Straughn
Attorney Docket Number:	48929.4008/US03
Receipt Date:	09-FEB-2022
Filing Date:	05-OCT-2021
Time Stamp:	15:33:36
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	Response to Election / Restriction Filed	48929-4008_US03_RespRR.pdf	131892 a09c801881690a3f9d4041be9afb119c1c841a86	no	8

Warnings:

Information:	
Total Files Size (in bytes):	131892

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

In re Application of:	Group Art Unit: 1631
PERSONALIS, INC.	Examiner: Joseph T. Woitach
Serial No.: 17/494,513	Customer No. 182685
Filed: October 5, 2021	Confirmation No. 8186
For: **METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN**	Attorney Docket No. 48929.4008/US03

Filed via EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO RESTRICTION REQUIREMENT

Commissioner:

This communication is responsive to the Restriction Requirement of October 13, 2021. Applicants submit this response on or before March 7, 2022, making it timely.

Amendments to the Claims begins on page 2 of this paper; and

Remarks begin on page 6 of this paper.

Certificate of EFS-Web Transmission

Date: February 9, 2021

I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO.

/Sheila Gloss/
SHEILA GLOSS
4147-7770-5268.5

AMENDMENTS TO THE CLAIMS

The listing of claims will replace all prior versions and listing of claims in the application.

1-9. (Canceled)

10. (Withdrawn) A method of analyzing a biological sample obtained from a subject being screened for a disease, comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by independently sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, and wherein (i) said first set of nucleic acid molecules is extracted from a first component separated from a blood sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a second component separated from said blood sample;

(b) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants in said first set of sequence reads that is not present in said second set of sequence reads; and

(c) subsequent to (b), identifying one or more second mosaic variants in a second sample of said subject, wherein said second sample is obtained from a source or at a time point that is different than said blood sample.

11. (Withdrawn) The method of claim 10, further comprising identifying one or more third mosaic variants in a third sample of said subject, which third sample is obtained from a source or at a time point that is different than said blood sample and said second sample.

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12. (Withdrawn) The method of claim 10, further comprising providing a report and/or a therapeutic intervention based on an identification of said first mosaic variants or said second mosaic variants.

13. (Withdrawn) The method of claim 10, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

14. (Withdrawn) The method of claim 11, wherein said second or third sample comprises a blood sample, a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy, a saliva sample, a buccal swab, a urine sample, a semen sample, a cerebrospinal fluid sample, or a breast milk sample of said subject.

15. (Withdrawn) The method of claim 11, wherein said one or more first, second, or third mosaic variants are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

16. (Withdrawn) The method of claim 11, wherein said one or more first, second, or third mosaic variants are causal or predisposing for a disease.

17. (Withdrawn) The method of claim 11, wherein said one or more first, second, or third mosaic variants are non-causal for a disease.

18. (Withdrawn) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said blood sample, second sample, or third sample.

19. (Withdrawn) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said blood sample and said second sample or said third sample.

20. (Previously presented) A method for early disease detection in a subject, said method comprising:

(a) obtaining a blood sample from said subject;

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(b) extracting (i) a first set of nucleic acid molecules from a first component separated from a blood sample of said subject and (ii) a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample;

(c) quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules present in said first component separated from a blood sample;

(d) comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity;

(e) if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads generated by independently sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules;

(f) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants in said first set of sequence reads that is not present in said second set of sequence reads; and

(g) subsequent to (f), identifying one or more second mosaic variants in a second sample of said subject, which second sample is obtained from a source or at a time point that is different than said blood sample.

21. (Previously presented) The method of claim 20, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

22. (Previously presented) The method of claim 20, further comprising identifying one or more third mosaic variants in a third sample of said subject, which third sample is obtained from a source or at a time point that is different than said blood sample and said second sample.

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23. (Previously presented) The method of claim 20, wherein said second or third sample comprises a blood sample, a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy, a saliva sample, a buccal swab, a urine sample, a semen sample, a cerebrospinal fluid sample or a breast milk sample of said subject.

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REMARKS

Status of the claims

Claims 20-23 are currently pending. Claims 10-19 are withdrawn, and claims 1-9 are canceled. Applicants respectfully request entry of the amended claims.

Restriction Requirement

The Office requires the Applicants to elect one below identified inventions for continued prosecution on the merits. The inventions are:

- Group I, claims 10-19 are drawn to a method of analyzing a biological sample by comparing sequence reads obtained from a blood component and leukocytes.
- Group II, claims 20-23 are drawn to a method of early disease detection by comparing sequence reads from the blood of a subject.

Applicants herein **elect Group II, drawn to a method of early disease detection by comparing sequence reads from the blood of a subject** without traverse.

Claims 20-23 encompass the elected invention.

Species Election

The Office requires the Applicants to make an election for each of the species groupings identified below for continued prosecution on the merits. The species are:

- Species Group I, nucleic acid sample sources, claim 23 is drawn to a method wherein said second or third sample comprises a blood sample, a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy, a saliva sample, a buccal swab, a urine sample, a semen sample, a cerebrospinal fluid sample, or a breast milk sample of said subject.
- Species Group II, the type of variant being identified, claim 22 is drawn to a method wherein said one or more first, second, or third mosaic variants are

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selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

Applicants herein **elect "a blood sample" and "single nucleotide polymorphisms (SNPs)"** without traverse.

Claims 23 and 22 encompass the elected species, respectively.

Applicants reserve the right to rejoin any withdrawn claims should an elected claim be found allowable in view of the direct or indirect dependency of the claims on elected claims 20-23, under MPEP 809 and MPEP 821.04, and 37 CFR § 1.141(a).

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CONCLUSION

Prompt and favorable consideration of this Response is respectfully requested. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided below.

The Applicants reserve the right to pursue at a later date any previously pending or other claims that capture any subject matter supported by the present disclosure. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have disclaimed or disavowal any subject matter supported by the present application.

Except for issues fees payable under 37 CFR § 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees including fees due under 37 CFR § 1.16 and 1.17, which may be required, and including any required extension of time fees, or credit any overpayment to Deposit Account 15-0665 (Docket Reference: 48929.4008/US03).

Respectfully submitted,

Orrick, Herrington & Sutcliffe LLP

Dated: February 9, 2022

By: /Alex Straughn/
Alex Straughn
Reg. No. 80,155
Agent for Applicant

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Telephone: (949) 567-6700
Facsimile: (949) 567-6710

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 17/494,513	Filing Date 10/05/2021	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $50 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $240 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	02/09/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0		x $50 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $240 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TINA J BARDEN/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 01/07/2022

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
01/07/2022	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
vsantos@orrick.com

Office Action Summary	Application No. 17/494,513	Applicant(s) West, John	
	Examiner Joseph T Woitach	Art Unit 1631	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 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 11/15/2021.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 10-23 is/are pending in the application.

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

6) ☐ Claim(s) _____ is/are allowed.

7) ☐ Claim(s) _____ is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☑ Claim(s) 10-23 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

TrackOne Request

Applicants request filed 10/5/2021 has been granted (see paper mailed 12/8/2021).

Applicant's Amendment

Applicant's preliminary amendment filed 10/5/2021 has been received and entered. Claims 1-9 have been cancelled, and claims 11-23 have been added.

Claims 11-23 are pending.

Priority

This application filed 10/5/2021 is a Divisional of 16/132123, now US Patent 11142802, which is a continuation of 14/929075, now US Patent 10125399, which claims benefit to US provisional application 2/072936 filed 10/30/2014; and is related to 17/065406 filed 10/7/2020 through parent 16/132123, and to PCT/US15/58483 filed 10/30/2015.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 10-19, drawn to a method of analyzing a biological sample by comparing sequence reads obtained from a blood component and leukocytes.

II. Claims 20-23, drawn to a method of early disease detection by comparing sequence reads from the blood of a subject.

The inventions are independent or distinct, each from the other because:

Inventions I and II are directed to related methods. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are directed to methods with different recited steps and appear to result in unique types of information from practicing the steps as presently claimed. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Restriction for examination purposes as indicated is proper because all the inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

The search for the different claimed method steps and consideration for the ability to interpret and correlate the results require a different search and consideration for the two methods as presently set forth.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

For both methods, this application contains claims directed to the following patentably distinct species of:

-nucleic acid sample sources (see claim 14 for example); and

-the type of variant being identified (see claim 15 for example).

The species are independent or distinct because each provide a different search requirement, and different consideration for the claims as a whole for ability to obtain the data and what the data may represent in the final identification step of the claims. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, all claims are generic as they encompass or recite the different species.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply: the search for each species is different and unique, and subsequent steps for analysis require separate consideration for what the data represents and importance for interpretation/correlation.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should

submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph T Woitach whose telephone number is (571)272-0739. The examiner can normally be reached Mon-Fri; 9:00-5:00.

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, Karlheinz R Skowronek can be reached on 571 272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more

information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Joseph Woitach/
Primary Examiner, Art Unit 1631

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/494,513	10/05/2021	John West	48929.4008/US03	8186

182685 7590 12/08/2021

ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

EXAMINER
CENTRAL, DOCKET

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
12/08/2021	ELECTRONIC

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

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipprosecution@orrick.com
vsantos@orrick.com

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Foresight v Personalis
IPR2024-00170

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 17/494,513	**Applicant(s)** West, John	
	Examiner ANGELA E WALKER	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 05 October 2021 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 ANGELA WALKER at (571) 272-1058. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/ANGELA E WALKER/ Paralegal Specialist, OPET	

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :C47345

Sale Accounting Date:12/07/2021

Sale Item Reference Number	Effective Date
17494513	10/05/2021

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I2021B7D33563019	2830	PROCESSING FEE, EXCEPT PROV. APPLS.	$70.00	Deposit Account

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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
17/494,513	10/05/2021	1636	830	48929.4008/US03	14	2

CONFIRMATION NO. 8186

UPDATED FILING RECEIPT

182685
ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

OC000000129849415

Date Mailed: 11/17/2021

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)

John West, Cupertino, CA;

Applicant(s)

Personalis, Inc., Menlo Park, CA;

Power of Attorney: The patent practitioners associated with Customer Number 182685

Domestic Priority data as claimed by applicant

This application is a DIV of 16/132,123 09/14/2018 PAT 11142802
which is a CON of 14/929,075 10/30/2015 PAT 10125399
which claims benefit of 62/072,936 10/30/2014

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.

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If Required, Foreign Filing License Granted: 10/18/2021

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/494,513**

Projected Publication Date: 02/24/2022

Non-Publication Request: No

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

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Preliminary Class

435

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign 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).

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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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/494,513

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	80		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	350		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	400		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	14 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 240 =	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	830		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
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	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/494,513	10/05/2021	John West	48929.4008US03

CONFIRMATION NO. 8186

182685
ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

FORMALITIES LETTER

OC000000129174160

Date Mailed: 10/19/2021

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

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

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

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings submitted to the Office are not electronically reproducible because portions of figures 1, 5 are missing and/or blurry.

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

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IPR2024-00170

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**.

/myclaros-blanco/

Foresight EX1108-p. 377
Foresight v Personalis
IPR2024-00170

Electronic Acknowledgement Receipt

EFS ID:	44284722
Application Number:	17494513
International Application Number:	
Confirmation Number:	8186
Title of Invention:	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN
First Named Inventor/Applicant Name:	John West
Customer Number:	182685
Filer:	Gargi Talukder/Jodie Davis
Filer Authorized By:	Gargi Talukder
Attorney Docket Number:	48929.4008US03
Receipt Date:	15-NOV-2021
Filing Date:	05-OCT-2021
Time Stamp:	18:08:13
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	Applicant Response to Pre-Exam Formalities Notice	Personalis_4008_US03_Transmittal_Response_to_Missing_Parts_Corrected_Drawings.pdf	150345 6b5e2bd8109ea77011de6a409d2052b99e02cf49	no	3

Warnings:

Information:					
2	Drawings-only black and white line drawings	Personalis_4008_US03_Corrected_Figs_1_and_5pdf.pdf	42665 5f3f890eca59bef3391d301f55e4fe3e3cbee5bf	no	2
Warnings:					
Information:					
3	Applicant Response to Pre-Exam Formalities Notice	Personalis_4008_US03_Notice_To_File_Corrected_Appln_Papers.pdf	59564 dd249750412db8114cdd5438f2a19f0e598f80c8	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	252574		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	17/494,513	Confirmation No.: 8186
Applicant	:	Personalis, Inc.	
Filing Date	:	October 5, 2021	
Title	:	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN	
Group Art Unit	:	1636	
Examiner	:	Unassigned	
Docket No.	:	48929.4008/US03	
Customer No.	:	34313	

EFS Web
Commissioner for Patents

TRANSMITTAL OF MISSING PARTS AND/OR RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Sir:

1. DOCUMENTS ENCLOSED:

In response to the **NOTICE TO FILE MISSING PARTS OF APPLICATION UNDER 37 CFR § 1.53(b)** and/or **NOTICE TO FILE CORRECTED APPLICATION PAPERS**, which was mailed by the Patent Office on October 19, 2021, enclosed are:

- ☐ Declaration
- ☐ Power of Attorney: ☐ Separate or ☐ Combined with Declaration
- ☐ Statement Under 37 CFR § 3.73(b)
- ☐ Replacement Specification (_____ pages). Replacement sheets contain no new matter.

Certificate of EFS-Web Transmission

Date: November 15, 2021

I hereby certify that this correspondence is being transmitted via the U.S. Patent and Trademark Office electronic filing system (EFS-Web) to the USPTO.

/Jodie Davis/
JODIE DAVIS
4165-4534-0944

☒ Formal Drawings (_2_ pages). Replacement sheets contain no new matter.

☒ A copy of the Notice to File Missing Parts of Application under 37 CFR § 1.53(b) and/or Notice to File Corrected Application Papers.

3. STATEMENT UNDER 37 CFR 1.52(d) - ENGLISH LANGUAGE TRANSLATION

☐ This is application was filed in a language other than English;

☐ English language translation is attached herewith;

☐ Applicant(s) hereby confirms that the translation is accurate, and no new matter has been added.

☐ Processing fee of $140 (1.17(i)) is included.

3. REQUEST FOR EXTENSION OF TIME:

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply.

☐ Applicant(s) petitions for an extension of time under 37 CFR § 1.136 [fees: 37 CFR § 1.17(a)(1)-(5)] for the total number of months checked below:

EXTENSION (months)	FEE FOR LARGE ENTITY	FEE FOR SMALL ENTITY	FEE FOR MICRO ENTITY
☐ one month	$220.00	$110.00	$55.00
☐ two months	$640.00	$320.00	$160.00
☐ three months	$1,480.00	$740.00	$370.00
☐ four months	$2,320.00	$1,160.00	$580.00
☐ five months	$3,160.00	$1,580.00	$790.00
			Fee 0.00

☒ If any extension fee is required, please consider this a petition therefore.

4. FILING FEES

☐ Applicant claims small entity status pursuant to 37 CFR 1.27.

Basic Filing Fee							$320.00
Search Fee							$700.00
Examination Fee							$800.00
Total Claims	24	-	20	=	4	x $100.00	$208.00
Independent Claims	5	-	3	=	2	x $480.00	$840.00

Application Size Fee ($400 for each additional 50 sheets or fraction thereof)		- 100 =	0	x $420.00	$0.00
Multiple Dependent Claims	$860	(if applicable)	☐		$0.00
Surcharge 37 CFR § 1.16(e)	$320	(if applicable)	☒		$0.00
TOTAL OF ABOVE CALCULATIONS					$00.00
☐ Reduction by ½ for Filing by Small Entity. Note 37 CFR §§ 1.9, 1.27, 1.28.					$00.00
☐ Reduction by ¾ for Filing by Micro Entity. Note 37 CFR §1,29(a)(d)					$00.00
☐ Reduction for electronic filing for small entities					-$75.00
TOTAL FEES SUBMITTED HEREWITH					$00.00

4. Method of Payment of fees:

☐ A check in the amount of $_____ is enclosed to cover the above fee(s).

☐ Charge Orrick's Deposit Account No. **15-0665** in the amount of **$_____**.

☒ The Commissioner is authorized to charge Orrick's Deposit Account No. **15-0665** for any fees required under 37 CFR §§ 1.16 and 1.17 that are not covered, in whole or in part, by a check enclosed herewith and to credit any overpayments to said Deposit Account No. **15-0665**.

Respectfully submitted,
ORRICK, HERRINGTON & SUTCLIFFE LLP

Dated: November 15, 2021

By: /Gargi Talkuder/
Gargi Talkuder
Reg. No. 61,368

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Tel: 949-567-6700
Fax: 949-567-6710
Customer Number: 34313

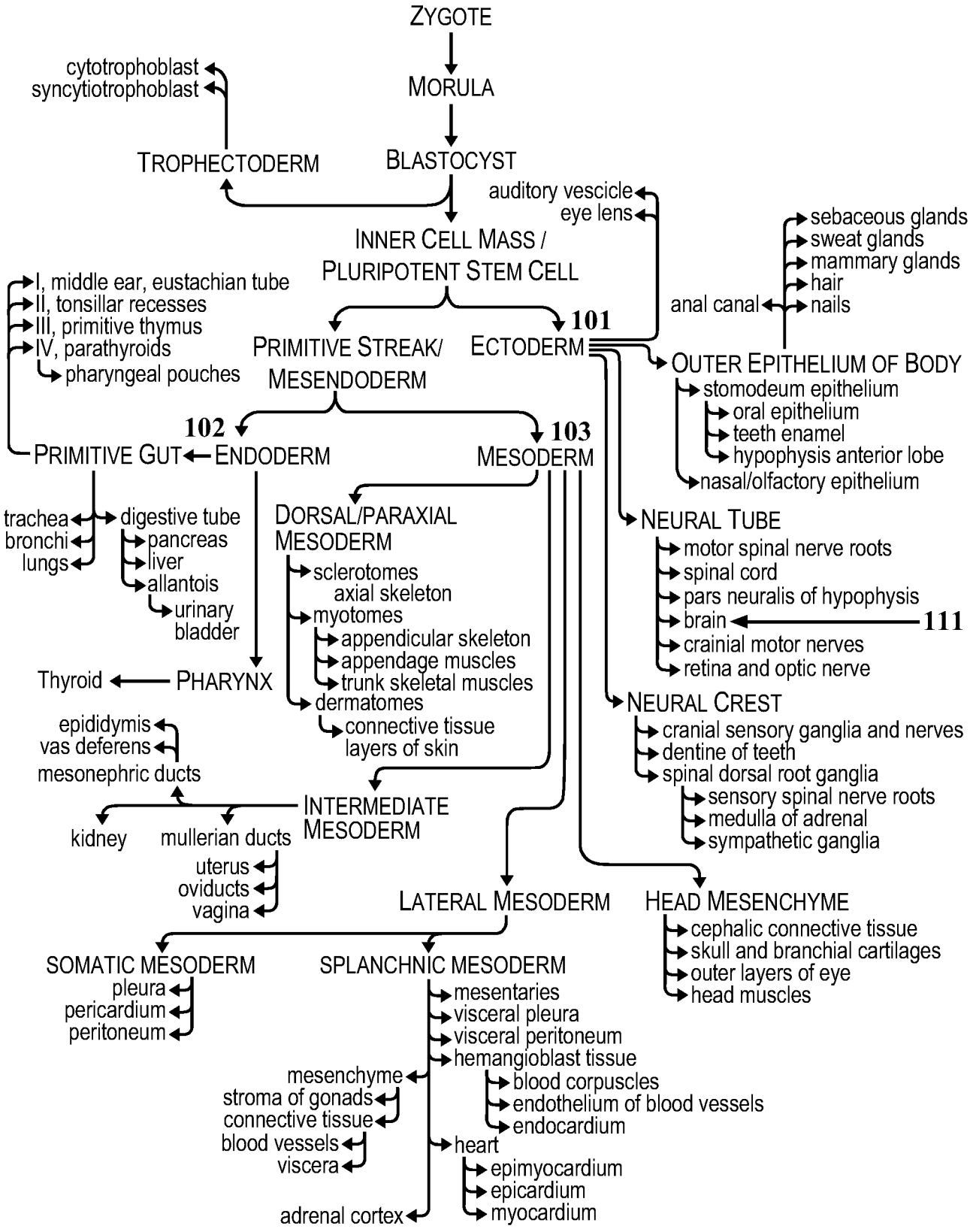

ZYGOTE
MORULA
BLASTOCYST
cytotrophoblast
syncytiotrophoblast
TROPHECTODERM
INNER CELL MASS / PLURIPOTENT STEM CELL
auditory vesicle
eye lens
sebaceous glands
sweat glands
mammary glands
hair
anal canal
nails
I, middle ear, eustachian tube
II, tonsillar recesses
III, primitive thymus
IV, parathyroids
pharyngeal pouches
PRIMITIVE STREAK/ MESENDODERM
101
ECTODERM
OUTER EPITHELIUM OF BODY
stomodeum epithelium
oral epithelium
teeth enamel
hypophysis anterior lobe
nasal/olfactory epithelium
102
103
PRIMITIVE GUT
ENDODERM
MESODERM
trachea
bronchi
lungs
digestive tube
pancreas
liver
allantois
urinary bladder
DORSAL/PARAXIAL MESODERM
sclerotomes
axial skeleton
myotomes
appendicular skeleton
appendage muscles
trunk skeletal muscles
dermatomes
connective tissue layers of skin
NEURAL TUBE
motor spinal nerve roots
spinal cord
pars neuralis of hypophysis
brain
111
crainial motor nerves
retina and optic nerve
Thyroid
PHARYNX
NEURAL CREST
cranial sensory ganglia and nerves
dentine of teeth
spinal dorsal root ganglia
sensory spinal nerve roots
medulla of adrenal
sympathetic ganglia
epididymis
vas deferens
mesonephric ducts
INTERMEDIATE MESODERM
kidney
mullerian ducts
uterus
oviducts
vagina
LATERAL MESODERM
HEAD MESENCHYME
cephalic connective tissue
skull and branchial cartilages
outer layers of eye
head muscles
SOMATIC MESODERM
pleura
pericardium
peritoneum
SPLANCHNIC MESODERM
mesentaries
visceral pleura
visceral peritoneum
hemangioblast tissue
mesenchyme
stroma of gonads
connective tissue
blood vessels
viscera
blood corpuscles
endothelium of blood vessels
endocardium
heart
epimyocardium
epicardium
myocardium
adrenal cortex

FIG. 1

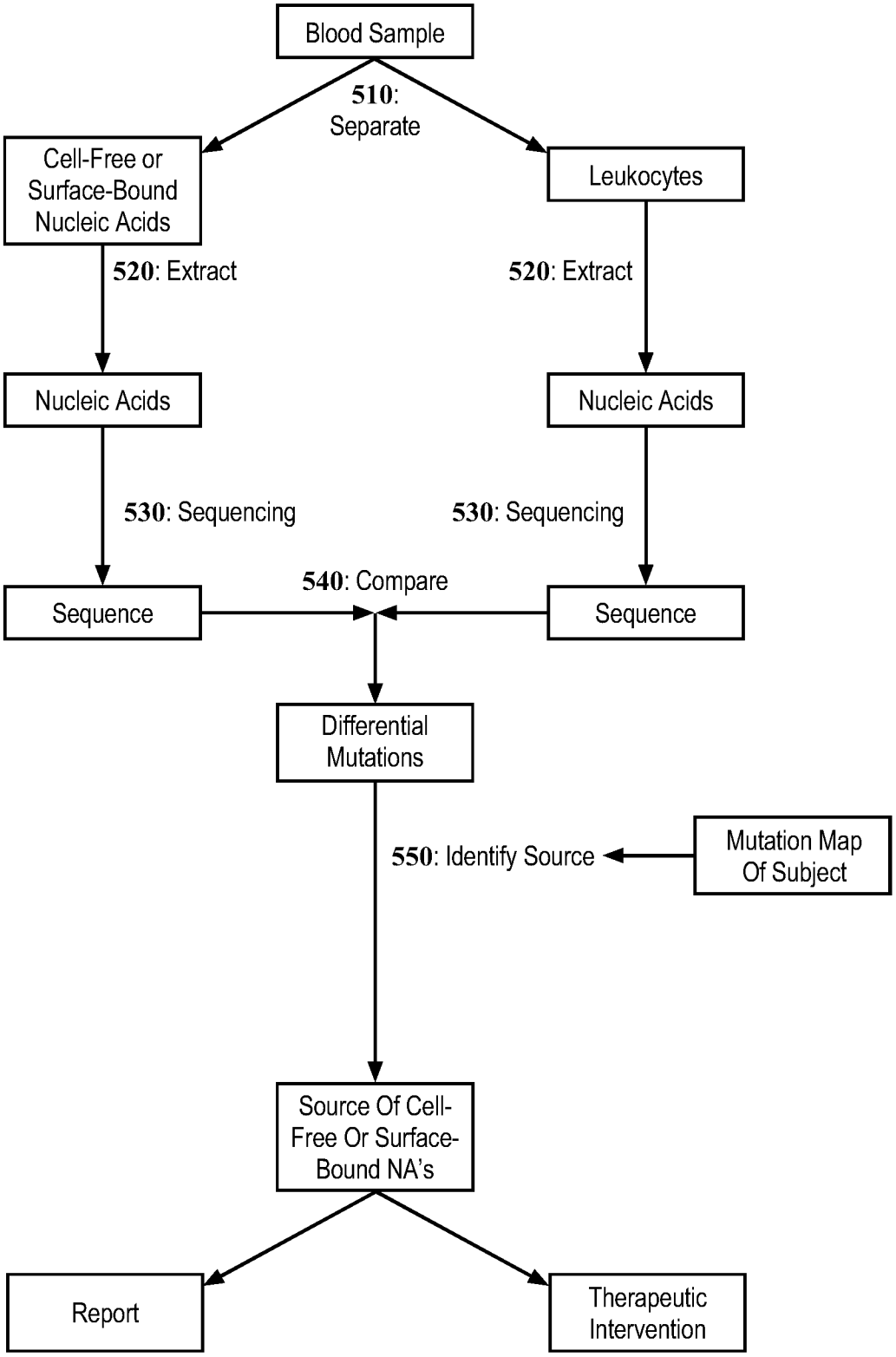

Blood Sample
510: Separate
Cell-Free or Surface-Bound Nucleic Acids
Leukocytes
520: Extract
520: Extract
Nucleic Acids
Nucleic Acids
530: Sequencing
530: Sequencing
540: Compare
Sequence
Sequence
Differential Mutations
550: Identify Source
Mutation Map Of Subject
Source Of Cell-Free Or Surface-Bound NA's
Report
Therapeutic Intervention

FIG. 5

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/494,513

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	80		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	350		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	400		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	14 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 240 =	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	830		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/494,513	10/05/2021	John West	48929.4008US03

CONFIRMATION NO. 8186

182685
ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

FORMALITIES LETTER

OC00000129174160

Date Mailed: 10/19/2021

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

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

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

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings submitted to the Office are not electronically reproducible because portions of figures 1, 5 are missing and/or blurry.

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

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Foresight v Personalis
IPR2024-00170

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**.

/myclaros-blanco/

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Foresight v Personalis
IPR2024-00170

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/494,513	10/05/2021	1636	830	48929.4008US03	14	2

CONFIRMATION NO. 8186

FILING RECEIPT

182685
ORRICK, HERRINGTON & SUTCLIFFE LLP (Personalis)
IP Prosecution
2050 Main Street, Suite 1100
IRVINE, CA 92614

OC000000129174159

Date Mailed: 10/19/2021

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)

John West, Cupertino, CA;

Applicant(s)

Personalis, Inc., Menlo Park, CA;

Power of Attorney: The patent practitioners associated with Customer Number 182685

Domestic Priority data as claimed by applicant

This application is a DIV of 16/132,123 09/14/2018 PAT 11142802
which is a CON of 14/929,075 10/30/2015 PAT 10125399
which claims benefit of 62/072,936 10/30/2014

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.

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Foresight v Personalis
IPR2024-00170

If Required, Foreign Filing License Granted: 10/18/2021

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/494,513**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

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

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

Preliminary Class

435

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign 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).

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Foresight v Personalis
IPR2024-00170

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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

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

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

NOT GRANTED

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

SelectUSA

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

Foresight EX1108-p. 390
Foresight v Personalis
IPR2024-00170

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:	John West	Nonprovisional Application Number (if known):	
Title of Invention:	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin		

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 /Gargi Talukder/	Date October 5, 2021
Name (Print/Typed) Gargi Talukder	Practitioner Registration Number 61,368

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	48929.4008US03
	Application Number	
Title of Invention	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin	

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
	John		West	

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

City	State/Province	Country of Residence
Cupertino	CA	US

Mailing Address of Inventor:

Address 1	1330 O'Brien Drive
Address 2	

City	State/Province	Postal Code	Country
Menlo Park	CA	94025	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	182685		
Email Address	ipprosecution@orrick.com	Add Email	Remove Email

Application Information:

Title of the Invention	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin		
Attorney Docket Number	48929.4008US03	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	6	Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	48929.4008US03
	Application Number	
Title of Invention	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin	

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	182685		

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)
	Division of	16/132123	2018-09-14

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	48929.4008US03
	Application Number	
Title of Invention	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin	

Prior Application Status	Patented	Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/132123	Continuation of	14/929075	2015-10-30	10125399	2018-10-24

Prior Application Status	Expired	Remove

Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
14/929075	Claims benefit of provisional	62/072936	2014-10-30

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

Foreign Priority Information:

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

Remove

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

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

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	48929.4008US03
	Application Number	
Title of Invention	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin	

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	48929.4008US03
	Application Number	
Title of Invention	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin	

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	Personalis, Inc.		
Mailing Address Information For Applicant:			
Address 1	1330 O'Brien Drive		
Address 2			
City	Menlo Park	**State/Province**	CA
Country	US	Postal Code	94025
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	48929.4008US03
	Application Number	
Title of Invention	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin	

Assignee 1

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

Remove

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

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

Mailing Address Information For Assignee including Non-Applicant Assignee:

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

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

Signature:

Remove

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

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

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

Signature	/Gargi Talukder/			Date (YYYY-MM-DD)	2021-10-05
First Name	Gargi	Last Name	Talukder	Registration Number	61368

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

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	Application Number	
Title of Invention	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin	

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

Privacy Act Statement

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

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

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

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

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	2021-10-05
First Named Inventor	John West
Art Unit	
Examiner Name	
Attorney Docket Number	48929.4008US03

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	10125399		2018-11-13	John West	
	2	9128861		2015-09-08	Gabor T. Bartha, et al.	
	3	7803550		2015-09-08	Vladimir L. Makarov, et al.	
	4	6582938		2003-06-24	Xing Su, et al.	
	5	6015674		2000-01-18	Timothy M. Woudenberg, et al.	
	6	5928907		1999-07-27	Timothy M. Woudenberg, et al.	
	7	5641658		1997-06-24	Christopher P. Adams, et al.	
	8	5494810		1996-02-27	Francis Barany, et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2021-10-05
	First Named Inventor	John West
	Art Unit	
	Examiner Name	
	Attorney Docket Number	48929.4008US03

	9	5299491		1994-04-05	Kazuki Kawada	
	10	5242794		1993-09-07	Norman M. Whiteley, et al.	
	11	4988617		1991-01-29	Ulf Landegren, et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20210062276		2021-03-04	John West	
	2	20140200147		2014-07-17	Gabor T. Bartha, et al.	
	3	20120058480		2012-03-08	Dorothy E. Lewis, et al.	
	4	20050260645		2005-11-24	Roland D. Green, et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2021-10-05
	First Named Inventor	John West
	Art Unit	
	Examiner Name	
	Attorney Docket Number	48929.4008US03

	1	EP 3212808	EP		2017-09-06	John West		
	2	WO2016070131	WO		2016-05-06	Personalis, Inc. (US)		
	3	WO 0018957	WO		2000-04-06	Applied Research Systems (NL), et al.		

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	ADESSI, et al. Solid phase DNA amplification: characterisation of primer attachment and amplification mechanisms. Nucleic Acids Res. 2000 Oct 15;28(20):E87.	
	2	ARRUDA et al. Capturing intra-tumor genetic heterogeneity by de novo mutation profiling of circulating cell-free tumor DNA: a proof-of-principle. Annals of oncology 25.9 (2014): 1729-1735.	
	3	BAIRD, et al. Developing recombinant antibodies for biomarker detection. Cancer Biomark. 2010;6(5-6):271-9. doi: 10.3233/CBM-2009-0144.	
	4	BECK, et al. Profile of the circulating DNA in apparently healthy individuals. Clin Chem. 2009 Apr;55(4):730-8. doi: 10.1373/clinchem.2008.113597. Epub 2009 Jan 30.	
	5	BEHJATI, et al. Genome sequencing of normal cells reveals developmental lineages and mutational processes. Nature. 2014 Sep 18;513(7518):422-5. doi: 10.1038/nature13448. Epub 2014 Jun 29.	
	6	BIESECKER, et al. A genomic view of mosaicism and human disease. Nat Rev Genet. 2013 May;14(5):307-20. doi: 10.1038/nrg3424.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	2021-10-05
	First Named Inventor	John West
	Art Unit	
	Examiner Name	
	Attorney Docket Number	48929.4008US03

	7	BISCHOFF, et al. Cell-free fetal DNA and intact fetal cells in maternal blood circulation: implications for first and second trimester non-invasive prenatal diagnosis. Hum Reprod Update. 2002 Nov-Dec;8(6):493-500.	
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CERTIFICATION STATEMENT

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

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SIGNATURE

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Name/Print	Gargi Talukder	Registration Number	61,368

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin
First Named Inventor/Applicant Name:	John West
Filer:	Gargi Talukder/Michelle Marsh
Attorney Docket Number:	48929.4008US03

Filed as Small Entity

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	80	80
UTILITY SEARCH FEE	2111	1	350	350
UTILITY EXAMINATION FEE	2311	1	400	400
REQUEST FOR PRIORITIZED EXAMINATION	2817	1	2100	2100
Pages:				
Claims:				
Miscellaneous-Filing:				
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2930**

Electronic Acknowledgement Receipt

EFS ID:	43953851
Application Number:	17494513
International Application Number:	
Confirmation Number:	8186
Title of Invention:	Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin
First Named Inventor/Applicant Name:	John West
Customer Number:	182685
Filer:	Gargi Talukder/Michelle Marsh
Filer Authorized By:	Gargi Talukder
Attorney Docket Number:	48929.4008US03
Receipt Date:	05-OCT-2021
Filing Date:	
Time Stamp:	17:13:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$2930
RAM confirmation Number	E202105H13361423
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	48929_4008US03_Track_One_Request.pdf	114777 9162aa307abb80901fb82244820a74c250be8283	no	2
Warnings:					
Information:					
2	Application Data Sheet	48929_4008US03_ADS.pdf	1260226 941a1b0e24766f721d1f630032b9684c0f10c507	no	8
Warnings:					
Information:					
3		48929_4008US03_Preliminary_Amendment.pdf	127254 03c0d747960dc9d72cfe12eb1886cc9bef9e72b1	yes	6

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:					
Information:					
4		48929_4008US03_Specification.pdf	20166119 82a96954934adf9e0b86c3ffbdf1023f58e9621d	yes	71

Multipart Description/PDF files in .zip description

Document Description	Start	End

	Specification		1	69	
	Claims		70	70	
	Abstract		71	71	
Warnings:					
Information:					
5	Drawings-only black and white line drawings	48929_4008US03_Drawings.pdf	1900549 67c3e1cb3b228671db3b92aa3a19bab76faee244	no	6
Warnings:					
Information:					
6	Power of Attorney	48929_4008US03_PowerOfAttorney.pdf	2777655 cb4c65d2295bf6191795b2a6c44fabca5d34046e	no	2
Warnings:					
Information:					
7	Assignee showing of ownership per 37 CFR 3.73	48929_4008US03_3-73c_Statement.pdf	114024 5e435362255eb15beb473db8bd13008f4b697374	no	3
Warnings:					
Information:					
8	Oath or Declaration filed	48929_4008US03_Declaration.pdf	269939 c89959d9c46b54ed467e7ae46d0afcea106ecd9d	no	2
Warnings:					
Information:					
9	Transmittal Letter	48929_4008US03_IDS_Transmittal.pdf	92793 fe3aa6c2d3f7a062bffe211279efea3cdc78e7b8	no	3
Warnings:					
Information:					
10	Information Disclosure Statement (IDS) Form (SB08)	48929_4008US03_IDS_SB08_1_of_2.pdf	1046808 a789ac43cba36faf6b582896acd3ea7309a2dbb7	no	10
Warnings:					
Information:					

11	Information Disclosure Statement (IDS) Form (SB08)	48929_4008US03_IDS_SB08_2_of_2.pdf	1045356 d77736c50e9ba6675e0987ac7e52d04f9e62a546	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
12	Fee Worksheet (SB06)	fee-info.pdf	48968 480aaf95e439822eaa7d1a9d259c201f7a89265e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	28964468	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/AIA/80 (07-17)
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

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

I hereby appoint:

[X] Practitioners associated with Customer Number: 182685

OR

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

Name	Registration Number

Name	Registration Number

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

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

[X] The address associated with Customer Number: 182685

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Personalis, Inc.
1330 O'Brien Drive
Menlo Park, CA 94025

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

SIGNATURE of Assignee of Record

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

Signature	Date 16 September 2021
Name Leslie Grab	Telephone 650-273-6299
Title Vice President of Intellectual Property	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

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

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: John West, et al.

Application No./Patent No.: TBD Filed/Issue Date: October 5, 2021

Titled: Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin

Personalis, 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 048094, Frame 0361, 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

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

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

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

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

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

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

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Gargi Talukder/	October 5, 2021
Signature	Date
Gargi Talukder	61,368
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

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

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
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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/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	METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

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 14/929,075

filed on October 30, 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: John West Date (Optional): 11/9/2016

Signature: John West

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.**

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	: **To be determined**	Confirmation No.:	**To be determined**
Applicant	: John WEST		
Filing Date	: October 5, 2021		
Title	: Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin		
Group Art Unit	: **To be determined**		
Examiner	: **To be determined**		
Docket No.	: 48929.4008US03		
Customer No.	: 182685		

EFS Web
Commissioner for Patents

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Sir:

In accordance with 37 CFR §§ 1.97 and 1.98, the items identified in this Information Disclosure Statement ("IDS") are brought to the attention of the Office. The items are listed on the attached forms PTO/SB/08a (PTO-1449). In accordance with the USPTO waiver of the requirement under 37 CFR § 1.98(a)(2)(i), only copies of foreign patent documents and non-patent literature are enclosed for the convenience of the Examiner.

The items identified in this IDS may or may not be "material" pursuant to 37 CFR § 1.56. The submission thereof by Applicant is not to be construed as an admission that any such patent, publication or other information referred to therein is material or considered to be material (37 CFR § 1.97(h)), or even qualifies as "prior art" under 35 USC § 102 with respect to this invention unless specifically designated by Applicant as such.

INFORMATION DISCLOSURE STATEMENT FILING PROVISION:

☒ This IDS is believed to be timely in that it is being submitted under 37 CFR § 1.97(b), that is (1) within three months of the filing date of the application, which is not a continued prosecution application filed under § 1.53(d); or (2) within three months of entry of the national stage as set forth in 37 CFR § 1.491; or (3) before the mailing of a first Office action on the merits; or (4) before the mailing of a first Office Action after filing a request for continued examination under 37 CFR § 1.114. Thus, no fee is required.

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☒ However, if the undersigned is in error in this regard, Applicant respectfully requests that the Office consider this IDS as filed under 37 CFR § 1.97(c), if applicable, and charge the fee due under 37 CFR §1.17(p) to the deposit account referenced below.

☐ However, if the undersigned is in error in this regard, Applicant respectfully requests that the Office consider this IDS as filed under 37 CFR § 1.97(c), if applicable, and a statement under 37 CFR § 1.97(e) is included below, thus no fee is required.

☐ This IDS is being submitted under 37 CFR § 1.97(c), that is after mailing of a first Office Action on the merits, but before a Final Action under 37 CFR § 1.113 or a Notice of Allowance under 37 CFR § 1.311.

☐ The fee due under 37 CFR § 1.17(p) is submitted herewith.

☐ A statement under 37 CFR § 1.97(e) is included below, thus no fee is required. In the event that this IDS is not received before a Final Action or a Notice of Allowance, then Applicant respectfully requests that the Office consider the filing of these papers to be submitted under 37 CFR § 1.97(d) and charge the fee due under 37 CFR § 1.17(p) to the deposit account below.

☐ This IDS is being submitted under 37 CFR § 1.97(d), that is after a Final Action under 37 CFR § 1.113 or a Notice of Allowance under 37 CFR § 1.311, but before payment of the issue fee. A statement under 37 CFR § 1.97(e) is included below. The fee due under 37 CFR § 1.17(p) is submitted herewith ($240.00) for large entity.

STATEMENT UNDER 37 CFR § 1.97(e):

☐ Each item contained in this IDS 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 this IDS.

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

Applicant	:	John West
Appl. No.	:	**To be determined**
Examiner	:	**To be determined**
Docket No.	:	48929.4008US03

STATEMENT UNDER 37 CFR § 1.98(d)(1):

☒ Copies of patents, publications, pending US applications or other information listed on the Information Disclosure Statement is NOT required, as such art was previously submitted in earlier application serial number 16/132,123. The subject application is a continuation, divisional, or continuation-in-part, and relies on the earlier application for an effective filing date under 35 USC § 120.

PAYMENT AND/OR AUTHORIZATION TO CHARGE FEES:

☐ A check in the amount of _____ is enclosed for the above fee(s).

☐ Please charge _____ to Deposit Account No. **15-0665** for the above fee(s).

☒ The Commissioner is authorized to charge any fees required by the filing of these papers, and to credit any overpayment to Orrick, Herrington & Sutcliffe's Deposit Account No. **15-0665** (File No.: 48929.4008US03).

Respectfully submitted,

ORRICK, HERRINGTON & SUTCLIFFE LLP

Dated: October 5, 2021 By: /Gargi Talukder/
Gargi Talukder
Reg. No. 61,368

ORRICK, HERRINGTON & SUTCLIFFE LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
949/567-6700 Telephone
949/567-6710 Facsimile

Customer No.: 182685

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: **To be determined**
John WEST	Art Unit: **To be determined**
U.S. Serial No.: **To be determined**	Confirmation No.: **To be determined**
Filing Date: **October 5, 2021**	Attorney Docket: **48929.4008US03**
For: **Methods for Using Mosaicism in Nucleic Acids Sampled Distal to Their Origin**	

Mail Stop AMENDMENT
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P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

Prior to the first office action, Applicant respectfully requests entry of the following amendments:

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 6 of this paper**.**

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AMENDMENTS TO THE SPECIFICATION

Paragraph [0001] of the specification should be replaced, as follows:

[0001] This application is a divisional application of U.S. Patent Application No. 16/132,123, filed September 14, 2018, which is a continuation of U.S. Patent Application No. 14/929,075, filed October 30, 2015 (now U.S. Patent No. 10,125,399), which claims priority to U.S. Provisional Patent Application No. 62/072,936, filed October 30, 2014, each of which is entirely incorporated herein by reference.

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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

1-9. (Canceled)

10. (New) A method of analyzing a biological sample obtained from a subject being screened for a disease, comprising:

(a) obtaining a first set of sequence reads and a second set of sequence reads by independently sequencing nucleic acid molecules derived from a first set of nucleic acid molecules and a second set of nucleic acid molecules, wherein said first set of sequence reads corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules, and wherein (i) said first set of nucleic acid molecules is extracted from a first component separated from a blood sample of said subject, and (ii) said second set of nucleic acid molecules is extracted from leukocytes from a second component separated from said blood sample;

(b) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants in said first set of sequence reads that is not present in said second set of sequence reads; and

(c) subsequent to (b), identifying one or more second mosaic variants in a second sample of said subject, wherein said second sample is obtained from a source or at a time point that is different than said blood sample.

11. (New) The method of claim 10, further comprising identifying one or more third mosaic variants in a third sample of said subject, which third sample is obtained from a source or at a time point that is different than said blood sample and said second sample.

12. (New) The method of claim 10, further comprising providing a report and/or a therapeutic intervention based on an identification of said first mosaic variants or said second mosaic variants.

13. (New) The method of claim 10, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

14. (New) The method of claim 11, wherein said second or third sample comprises a blood sample, a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a

biopsy, a core needle biopsy, a saliva sample, a buccal swab, a urine sample, a semen sample, a cerebrospinal fluid sample, or a breast milk sample of said subject.

15. (New) The method of claim 11, wherein said one or more first, second, or third mosaic variants are selected from the group consisting of: copy number variation, small insertions and deletions (inDels), single nucleotide polymorphisms (SNPs), multiple nucleotide polymorphisms (MNPs), and any combination thereof.

16. (New) The method of claim 11, wherein said one or more first, second, or third mosaic variants are causal or predisposing for a disease.

17. (New) The method of claim 11, wherein said one or more first, second, or third mosaic variants are non-causal for a disease.

18. (New) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said blood sample, second sample, or third sample.

19. (New) The method of claim 11, further comprising enriching said extracted nucleic acid molecules of said blood sample and said second sample or said third sample.

20. (New) A method for early disease detection in a subject, said method comprising:

(a) obtaining a blood sample from said subject;

(b) extracting (i) a first set of nucleic acid molecules from a first component separated from a blood sample of said subject and (ii) a second set of nucleic acid molecules from leukocytes from a second component separated from said blood sample;

(c) quantitating said first set of nucleic acid molecules to determine an amount of nucleic acid molecules present in said first component separated from a blood sample;

(d) comparing said amount of nucleic acid molecules present in said first component separated from a blood sample to a reference quantity;

(e) if said amount of nucleic acid molecules present in said first component separated from said blood sample is greater than or equal to a reference quantity, then obtaining a first set of sequence reads and a second set of sequence reads generated by independently sequencing nucleic acid molecules derived from said first set of nucleic acid molecules and said second set of nucleic acid molecules, wherein said first set of sequence reads

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corresponds to said first set of nucleic acid molecules and said second set of sequence reads corresponds to said second set of nucleic acid molecules;

(f) using said first set of sequence reads and said second set of sequence reads to identify one or more first mosaic variants in said first set of sequence reads that is not present in said second set of sequence reads; and

(g) subsequent to (f), identifying one or more second mosaic variants in a second sample of said subject, which second sample is obtained from a source or at a time point that is different than said blood sample.

21. (New) The method of claim 20, wherein said first component separated from said blood sample comprises cell-free or surface-bound nucleic acid molecules.

22. (New) The method of claim 20, further comprising identifying one or more third mosaic variants in a third sample of said subject, which third sample is obtained from a source or at a time point that is different than said blood sample and said second sample.

23. (New) The method of claim 20, wherein said second or third sample comprises a blood sample, a tissue sample, a benign tissue sample, a metastatic tissue sample, a mixed tissue sample, a biopsy, a core needle biopsy, a saliva sample, a buccal swab, a urine sample, a semen sample, a cerebrospinal fluid sample or a breast milk sample of said subject.

REMARKS

Status of the Claims

Claims 1-9 are cancelled. Claims 10-23 are new. Support for these claims can be found in the specification at paragraphs [0004]–[0007], [0013]–[0016], [0038], [0045], [0053], [0070], [0081], [0133], and [0200], and no new matter has been added. Entry of the amendment is respectfully requested.

The Commissioner is authorized to charge any additional required fees, including fees for extensions of time, or credit any overpayment to Orrick, Herrington & Sutcliffe LLP Deposit Account No. 15-0665 (File No.: 48929.4008US03).

Please direct any calls in connection with this application to the undersigned at (415) 773-5625.

Respectfully submitted,

ORRICK, HERRINGTON & SUTCLIFFE LLI

Dated: October 5, 2021

/Gargi Talukder/

Gargi Talukder, Reg. No. 61,368

Orrick, Herrington & Sutcliffe LLP
2050 Main Street, Suite 1100
Irvine, CA 92614-8255
Tel: 949-567-6700
Fax: 949-567-6710
Customer Number: 34313

METHODS FOR USING MOSAICISM IN NUCLEIC ACIDS SAMPLED DISTAL TO THEIR ORIGIN

CROSS-REFERENCE

[0001] This application is a continuation application of U.S. Patent Application No. 14/929,075, filed October 30, 2015, which claims priority to U.S. Provisional Patent Application No. 62/072,936, filed October 30, 2014, each of which is entirely incorporated herein by reference.

BACKGROUND

[0002] Many diseases may occur in locations of the body which are difficult to access without surgery or similarly invasive procedures. Thus it can be difficult to detect these diseases early, when a medical response may be most effective, and it can be difficult to monitor the progression of disease after it has been detected, especially if it requires screens which are expensive and/or invasive. In an attempt to respond to this challenge, many diagnostic tests in routine clinical use sample bodily fluids such as blood and urine which are easier to access, and analyze them for constituents reflective of the health status of the individual. In particular, the fluids may contain molecular or biological constituents which can be derived from multiple bodily locations (*see*, for example, Yahya et al., "The Clinical Utilization of Circulating Cell-Free DNA (CCFDNA) in Blood of Cancer Patients", International Journal of Molecular Sciences, 2013; Leary et al., "Detection of Chromosomal Alterations in the Circulation of Cancer Patients with Whole-Genome Sequencing", Science Translational Medicine, 2012; each of which is entirely incorporated herein by reference). However, when nucleic acids are detected in the body, distal from their source, there is no general method to know what the source tissue was. Thus if the quantity or other characteristic of the nucleic acids is indicative of disease, a physician may not know where the disease is located. In addition, because nucleic acids may have combined from many sources in the body, the sensitivity to detect a nucleic acid signal from any one part of the body may be limited by the presence of other nucleic acid signals from other parts of the body.

SUMMARY

[0003] The present disclosure provides methods for generating a mutation map for a subject and using the mutation map to determine the source of a given nucleic acid sequence or portion thereof in the subject. This may be used to determine, for example, the source of a disease in the subject, such as cancer. The source of the nucleic acid sequence or portion thereof may be determined by comparing the

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sequence to the mutation map. Examples of mutations maps include a spatial mutation map and a developmental mutation map.

[0004] Methods of the present disclosure can be used to detect and monitor a disease in a subject. For example, when nucleic acid molecules (also "nucleic acids" herein) are sampled distal from their sources in the body of a subject, the "nucleic acid signals" from many sources can be combined. Provided herein are methods to discriminate between these combined signals, so that they can be detected concurrently without mutual interference and without loss of information with respect to the source(s). This improves sensitivity and provides spatial localization of the source of each signal within the body.

[0005] An aspect provides a method for detecting differential mutations in a blood sample of a subject, comprising: a) separating the blood sample into at least a first component that includes cell-free or surface-bound nucleic acid molecules and a second component that includes leukocytes; b) extracting nucleic acid molecules from the first and second components; c) independently sequencing extracted nucleic molecules from the first and second components; and d) comparing with a programmed computer processor nucleic acid sequences of nucleic acid molecules of the first and second components to identify differential mutations.

[0006] In some embodiments, the method further comprises (e) identifying a source of the cell-free or surface-bound nucleic acid molecules based on the differential mutations. In some embodiments, the method further comprises providing a report. In some embodiments, the method further comprises providing a therapeutic intervention based on an identification of the source. In some embodiments, the report is provided on an electronic display having a user interface. In some embodiments, the source is identified as a tissue or group of tissues of the subject. In some embodiments, the method further comprises comparing the differential mutation(s) to a mutation map of the subject to identify the source. In some embodiments, the mutation map is a developmental mutation map. In some embodiments, the mutation map is a spatial mutation map. In some embodiments, the nucleic acid sequences of the extracted nucleic molecules from the first and second components are stored in computer memory.

[0007] In some embodiments, the method comprises identifying variants in nucleic acid molecules of the first component with respect to nucleic acid molecules of the second component. In some embodiments, the nucleic acid molecules of the second component are extracted by disrupting the leukocytes. In some embodiments, the nucleic acid molecules comprise deoxyribonucleic acid (DNA). In some embodiments, the cell-free or surface-bound nucleic acid molecules are cell-free DNA. In some

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embodiments, the cell-free or surface-bound nucleic acid molecules are surface-bound DNA. In some embodiments, the nucleic acid molecules comprise ribonucleic acid (RNA). In some embodiments, the nucleic molecules extracted from the first and second components are sequenced in a combined pool.

[0008] Another aspect provides a method for generating a mutation map of a subject that relates a mutation to a source of the mutation, comprising: a) obtaining nucleic acid samples from different tissues of the subject; b) sequencing nucleic molecules in the nucleic acid samples; c) identifying with a programmed computer processor differential mutations in nucleic acid sequences of nucleic acid molecules sequenced in (b); and d) generating in computer memory a relationship between the differential mutations and the different tissues to provide the mutation map of the subject.

[0009] In some embodiments, the mutation map is a developmental mutation map. In some embodiments, (d) of the method comprises (i) assigning the differential mutations on a developmental tree and (ii) generating the developmental mutation map from the developmental tree. In some embodiments, the developmental mutation map is generated using a hierarchical tree clustering algorithm.

[0010] In some embodiments, the mutation map is a spatial mutation map. In some embodiments, (d) of the method comprises (i) assigning the differential mutations on a spatial tree and (ii) generating the spatial mutation map from the body spatial map. In some embodiments, the spatial mutation map is generated using a hierarchical tree clustering algorithm.

[0011] In some embodiments, the method further comprises providing a report with the mutation map (e.g., developmental mutation map and/or spatial mutation map). In some embodiments, the report is provided on an electronic display having a user interface. In some embodiments, the nucleic acid sequences of the nucleic acid molecules sequenced in (c) are stored in computer memory. In some embodiments, (c) in the method comprises identifying variants in the nucleic acid sequences. In some embodiments, the blood sample is a whole blood sample. In some embodiments, the nucleic acid molecules comprise deoxyribonucleic acid (DNA). In some embodiments, the nucleic acid molecules comprise ribonucleic acid (RNA). In some embodiments, the nucleic molecules extracted from the biological samples are sequenced in a combined pool. In some embodiments, the nucleic acid samples are obtained from a blood sample of the subject.

[0012] In some embodiments, the sequencing comprises whole genome sequencing. In some embodiments, the sequencing comprises targeted genome sequencing. In some embodiments, the sequencing comprises untargeted genome sequencing. In some embodiments, the untargeted genome

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sequencing comprises whole genome sequencing. In some embodiments, the targeted sequencing includes at least one mutational hotspot. In some embodiments, the sequencing comprises redundant sequencing. The redundant sequencing can be duplex sequencing, Safe-SeqS or circular sequencing.

[0013] In some embodiments, the nucleic acid samples are obtained from at least one tissue with increased apoptosis. In some embodiments, the method further comprises inducing the increased apoptosis by one or more conditions selected from the group consisting of physical stress, targeted drugs, radiation and heat. In some embodiments, at least a subset of the nucleic acid samples are obtained from a blood sample, saliva sample, buccal swab, urine sample, semen sample, spinal fluid sample, skin shave biopsy, colon needle biopsy, nasal mucosal biopsy, testicular needle biopsy, endometrial biopsy, nerve biopsy by root canal, gastric endoscopic biopsy, metastatic tumor or breast milk of the subject. In some embodiments, (a) of the method comprises obtaining a nucleic acid sample from blood drawn at a first location of the subject having relatively high concentrations of cell-free nucleic acid molecules from a given tissue and a second location having low concentrations of cell-free nucleic acid molecules from the given tissue. In some embodiments, the method further comprises identifying mutations specific to the given tissue through differential analysis of nucleic acid sequences generated at the first location and second location. In some embodiments, the different tissues are non-cancerous tissues. In some embodiments, at least a subset of the nucleic acid samples is obtained from a blood sample of the subject.

[0014] Another aspect provides a method for monitoring state(s) of health of one or more tissues of a subject, comprising: a) at least one nucleic acid molecule from a blood sample of the subject; b) sequencing the nucleic acid molecule to generate a nucleic acid sequence of the nucleic acid molecule; c) identifying one or more mutations in the nucleic acid sequence; and d) using a mutation map of the subject in computer memory, identifying with a programmed computer processor a tissue of the subject associated with the nucleic acid molecule based on the one or more mutations identified in (c).

[0015] In some embodiments, the method further comprises providing a report with the tissue identified in (d). In some embodiments, the report is provided on an electronic display having a user interface. In some embodiments, (c) of the method comprises identifying variants in the nucleic acid sequences. In some embodiments, the blood sample is a whole blood sample. In some embodiments, the nucleic acid molecules comprise deoxyribonucleic acid (DNA). In some embodiments, the nucleic acid molecules comprise ribonucleic acid (RNA). In some embodiments, the nucleic acid molecule is a cell-free nucleic

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acid molecule. In some embodiments, the nucleic acid molecule is a surface-bound nucleic acid molecule.

[0016] In some embodiments, the method further comprises determining a state of health of the tissue. In some embodiments, the state is determined by comparing a quantity of the nucleic acid molecule against a reference to identify a relative abundance of the nucleic acid molecule. In some embodiments, the reference is a reference quantity. In some embodiments, the state is determined by aligning the nucleic acid sequence or portion thereof to a genome of the subject to identify a location of the nucleic acid sequence or portion thereof, which location is indicative of the state. In some embodiments, the state is determined by comparing a nucleic acid sequence or portion thereof to a reference to determine an apoptotic pattern, necrotic pattern, or predetermined mutations. In some embodiments, the reference is a genome of the subject. In some embodiments, the method further comprises providing a report and/or a therapeutic intervention based on a determination of the state of health.

[0017] In some embodiments, the sequencing comprises whole genome sequencing. In some embodiments, the sequencing comprises targeted genome sequencing. In some embodiments, the sequencing comprises untargeted genome sequencing. In some embodiments, the untargeted genome sequencing comprises whole genome sequencing. In some embodiments, the targeted sequencing includes at least one mutational hotspot. In some embodiments, the sequencing comprises redundant sequencing. The redundant sequencing can be duplex sequencing, Safe-SeqS or circular sequencing. In some embodiments, the sequencing is with the aid of one or more primers selected for the one or more mutations. In some embodiments, the mutation map is a developmental mutation map. In some embodiments, the mutation map is a spatial mutation map.

[0018] In another aspect, a method is provided for identifying a tissue of origin of a tumor metastasis in a subject. The method comprises: a) sequencing at least one nucleic acid molecule from a tumor metastasis of the subject to generate a nucleic acid sequence of the at least one nucleic acid molecule; b) identifying one or more mutations in the nucleic acid sequence; and c) using a mutation map of the subject in computer memory, identifying with a programmed computer processor a tissue of the subject associated with the nucleic acid molecule based on the one or more mutations identified in (b), thereby identifying the tissue of origin. In some embodiments, the method may further comprise treating the subject. In some embodiments, the treating may comprise administering an anti-cancer agent to the subject that is selected based on the tissue of origin. In some embodiments, the mutation map may be a developmental mutation map. In some embodiments, the mutation map may be a spatial mutation map.

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In some embodiments, the at least one nucleic acid molecule may include deoxyribonucleic acid (DNA). In some embodiments, the at least one nucleic acid molecule may comprise ribonucleic acid (RNA).

[0019] Another aspect of the present disclosure provides a non-transitory computer-readable medium comprising machine-executable code that, upon execution by one or more computer processors, implements any of the methods above or elsewhere herein.

[0020] Another aspect of the present disclosure provides a computer system comprising one or more computer processors and a non-transitory computer-readable medium coupled thereto. The non-transitory computer-readable medium comprises machine-executable code that, upon execution by the one or more computer processors, implements any of the methods above or elsewhere herein.

[0021] 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

[0022] 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

[0023] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also "FIG." and "FIGs." herein), of which:

[0024] **FIG. 1** shows an exemplary developmental tree;

[0025] **FIG. 2** shows a diagram of binary tree of cell division starting with the zygote, but with a mutation that only affects one germ layer (in this case the mesoderm);

[0026] **FIG. 3** shows a flowchart of the method for generating a mutation map of a subject;

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[0027] FIG. 4 shows a flowchart of the method for monitoring state(s) of health of one or more tissues of a subject;

[0028] FIG. 5 shows a flowchart of the method for detecting differential mutations in a blood sample of a subject; and

[0029] FIG. 6 shows a computer control system that is programmed or otherwise configured to implement any of the methods provided herein.

DETAILED DESCRIPTION

[0030] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

[0031] The term "subject," as used herein, generally refers to an individual having at least one biological sample that is undergoing analysis. The subject can be undergoing analysis to diagnose, predict or monitor a health, health condition, or well-being of the subject, such as, for example, identify or monitor a disease condition (e.g., cancer) in the subject. The subject can have a sample that is undergoing analysis by a researcher or a service provider, such as a healthcare professional or other individual or entity that employs methods of the present disclosure to analyze the sample.

[0032] The term "nucleic acid" as used herein generally refers to a polymeric form of nucleotides of any length. Nucleic acids can include ribonucleotides, deoxyribonucleotides or peptide nucleic acids (PNAs), that comprise purine and pyrimidine bases, or other natural, chemically or biochemically modified, non-natural, or derivatized nucleotide bases. A nucleic acid can be single or double stranded. The backbone of the polynucleotide can comprise sugars and phosphate groups, as may typically be found in deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), or modified or substituted sugar or phosphate groups. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. The sequence of nucleotides may be interrupted by non-nucleotide components. Thus the terms nucleoside, nucleotide, deoxynucleoside and deoxynucleotide generally include analogs such as those described herein. These analogs are those molecules having some structural features in common with a naturally occurring nucleoside or nucleotide such that when incorporated into a nucleic acid or oligonucleotide sequence, they allow hybridization with a naturally occurring nucleic acid

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sequence in solution. Typically, these analogs are derived from naturally occurring nucleosides and nucleotides by replacing and/or modifying the base, the ribose, or the phosphodiester moiety. The changes can be tailor made to stabilize or destabilize hybrid formation or enhance the specificity of hybridization with a complementary nucleic acid sequence as desired. The nucleic acid molecule may be a DNA molecule. The nucleic acid molecule may be an RNA molecule. The nucleic acid molecule may be a synthetic molecule.

[0033] The term "mutation map," as used herein, generally refers to a representation that relates a mutation to a source (e.g., tissue) in the subject. For example, a mutation can be related to a source in a developmental tree, and thus the mutation map is a developmental mutation map. In some cases, the developmental mutation map can be a cell lineage map. As another example, a mutation can be related to a body spatial map, and thus the mutation map is a spatial mutation map.

[0034] The terms "variant or derivative of a nucleic acid molecule" and "derivative or variant of a nucleic acid molecule," as used herein, generally refer to a nucleic acid molecule comprising a polymorphism. The terms "variant or derivative of a nucleic acid molecule" or "derivative or variant of a nucleic acid molecule" may also refer to a nucleic acid product that is produced from one or more assays conducted on the nucleic acid molecule. For example, a fragmented nucleic acid molecule, hybridized nucleic acid molecule (e.g., capture probe hybridized nucleic acid molecule, bead bound nucleic acid molecule), amplified nucleic acid molecule, isolated nucleic acid molecule, eluted nucleic acid molecule, and enriched nucleic acid molecule are variants or derivatives of the nucleic acid molecule.

[0035] The terms "detectable label" or "label," as used herein, generally refer to any chemical moiety attached to a nucleotide, nucleotide polymer, or nucleic acid binding factor, wherein the attachment may be covalent or non-covalent. The label can be detectable and render the nucleotide or nucleotide polymer detectable to a user or a system operated by the user. The terms "detectable label" or "label" may be used interchangeably. Detectable labels that may be used in combination with the methods disclosed herein include, for example, a fluorescent label, a chemiluminescent label, a quencher, a radioactive label, biotin, quantum dot, gold, or a combination thereof. Detectable labels include luminescent molecules, fluorochromes, fluorescent quenching agents, colored molecules, radioisotopes or scintillants. Detectable labels also include any useful linker molecule (such as biotin, avidin, streptavidin, HRP, protein A, protein G, antibodies or fragments thereof, Grb2, polyhistidine, Ni^{2}+, FLAG tags, myc tags), heavy metals, enzymes (examples include alkaline phosphatase, peroxidase and

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luciferase), electron donors/acceptors, acridinium esters, dyes and calorimetric substrates. It is also envisioned that a change in mass may be considered a detectable label, as is the case of surface plasmon resonance detection.

[0036] The terms "bound", "hybridized", "conjugated", "attached", and "linked" can be used interchangeably and generally refer to the association of an object to another object. The association of the two objects to each other may be from a covalent or non-covalent interaction. For example, a capture probe hybridized nucleic acid molecule refers to a capture probe associated with a nucleic acid molecule. The capture probe and the nucleic acid molecule are in contact with each other. In another example, a bead bound nucleic acid molecule refers to a bead associated with a nucleic acid molecule.

[0037] The terms "target-specific", "targeted," and "specific" can be used interchangeably and generally refer to a subset of the genome that is a region of interest, or a subset of the genome that comprises specific genes or genomic regions. For example, the specific genomic regions can be a region that is guanine and cytosine (GC) rich. Targeted sequencing methods can allow one to selectively capture genomic regions of interest from a nucleic acid sample prior to sequencing. Targeted sequencing involves alternate methods of sample preparation that produce libraries that represent a desired subset of the genome or to enrich the desired subset of the genome. The terms "untargeted sequencing" or "non-targeted sequencing" can be used interchangeably and generally refer to a sequencing method that does not target or enrich a region of interest in a nucleic acid sample. The terms "untargeted sequence", "non-targeted sequence," or "non-specific sequence" generally refer to the nucleic acid sequences that are not in a region of interest or to sequence data that is generated by a sequencing method that does not target or enrich a region of interest in a nucleic acid sample. The terms "untargeted sequence", "non-targeted sequence" or "non-specific sequence" can also refer to sequence that is outside of a region of interest. In some cases, sequencing data that is generated by a targeted sequencing method can comprise not only targeted sequences but also untargeted sequences.

[0038] The term "cell-free," as used herein, generally refers to a material that is present in an environment external to a cell. Such environment can include blood, plasma, serum, urine, saliva, mucosal excretions, semen, sputum, stool and tears. For example, a cell-free nucleic acid molecule (e.g., a DNA or RNA molecule) can be a nucleic acid molecule that is circulating freely in a blood stream of a subject. Examples of cell-free nucleic acid molecules include cell-free DNA (cfDNA) and cell-free RNA (cfRNA), which can include single or double stranded DNA and RNA, respectively.

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Cell-free nucleic acids can be found in, without limitation, blood, serum, cerebrospinal fluid (CSF), breast milk, urine, semen, and saliva.

[0039] The term "surface-bound" generally refers to a molecule that is bound, either specifically or non-specifically, to a surface. In some cases, "cell-bound" may be used interchangeably and may refer to a molecule that is bound, specifically or non-specifically, to the surface of a cell. In some cases, what is bound to the surface of the cell is a nucleic acid molecule. The surface of a cell may be "sticky" and may non-specifically bind nucleic acid molecules. In some cases, the cell in which the nucleic acid molecule is bound is also the cell in which the nucleic acid molecule was produced. In other cases, the cell in which the nucleic acid molecule is bound is not the cell in which the nucleic acid molecule was produced. "Surface-bound" or "cell-bound" nucleic acids can be isolated from the surface of which they are bound. "Cell-bound" nucleic acids can be bound to essentially any cell. In particular, cell-bound nucleic acids can be bound to blood cells (erythrocytes, leukocytes), circulating fetal cells, circulating endothelial cells, circulating tumor cells, and the like.

Genetic mosaicism and mutation maps

[0040] This present disclosure provides the methods for monitoring, diagnosing, and/or detecting diseases in a subject, such as a human subject, by detecting genetic variations in the subject. In some cases, the genetic variations may include many types of genetic variation, such as aneuploidy (e.g. full or partial trisomy), uniparental disomy at the level of entire or parts of chromosomes, chromosomal abnormalities (e.g., ring chromosomes), structural variation (e.g., large deletions, duplications, translocations, inversions, etc.), small insertions and deletions (e.g., inDels), and single and multiple nucleotide polymorphisms (SNP and MNP).

[0041] This disclosure also provides the methods for detecting genetic mosaicism. In some cases, a subject may be diagnosed with a disease if one or more mosaic variants are detected (*see*, for example, Biesecker et al., "A genomic view of mosaicism and human disease", Nature Reviews Genetics, 2013; which is entirely incorporated herein by reference). For example, the technologies used for detecting genetic mosaicism may include karyotyping, fluorescent in-situ hybridization (FISH), chromosome painting, Sanger sequencing, array comparative genomic hybridization (aCGH), SNP arrays, next generation DNA sequencing and redundant sequencing (e.g., Duplex sequencing, Safe-SeqS, Circle sequencing).

[0042] The methods may comprise constructing a mutation map unique for each individual. In some cases, constructing the mutation map comprise mapping the genetic variations (e.g. mutations) to one or

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more organs and/or tissues. The mutation map may relate a mutation to a tissue and/or an organ in the subject. The mutation map can be a spatial mutation map, a developmental mutation map, or a variant or combination thereof.

[0043] In some cases, the methods disclosed herein may include generating a developmental mutation map. The developmental mutation map may be specific for an individual subject. The developmental mutation map may be generated by sampling various tissues of a subject, identifying differential mutations that occur within those various tissues, and mapping the identified mutations onto a developmental tree. As shown in the developmental tree of **FIG. 1**, each cell in the adult human body is derived from the original zygote by a series of cell divisions. Like a tree diagram, the development of an embryo starts with the zygote as the trunk, and then advances from branch point to branch point. Along the path each cell becomes increasingly differentiated in multiple stages. Early on, cells separate off from the main cell mass to become the germ line and the extra-embryonic tissues (e.g. the placenta). Later, after expansion to about 200 cells, an event called gastrulation divides the cell mass into three germ layers: Ectoderm (**101**), Endoderm (**102**) and Mesoderm (**103**). As the process continues, further differentiation and branching occurs. For example, the Ectoderm is the source for the neurons of the brain (**111**), the epidermal cells of the skin, and the pigment cells (melanocytes), among others.

[0044] When a post-zygotic mutation occurs, it is inherited by all of the cells "downstream" along the developmental tree. Depending on how far along that is, the affected downstream tissues may be localized, both spatially and in terms of cell type. On the other hand, a mutation which is post-zygotic, but prior to gastrulation, can have downstream progeny in all three germ layers and ultimately in all tissues of the body. They may be present there in equal fractions, or in very different fractions, depending on how many variant cells progressed down each branch of the developmental tree. In another example, when a mutation occurs in a cell post-gastrulation (i.e., after formation of the three germ layers), this mutation may exist in all of the downstream cells, but may be restricted to the germ layer of the cell from which the mutation originated. For example, **FIG.2** depicts the development of a zygote **200** from a single cell to multiple progeny cells. A mutation that occurs in a cell post-gastrulation **210** will be present in all of the downstream cells **220, 230, 240**. As the originating cell is a mesoderm cell, the mutation will only occur in cells derived from the mesoderm (e.g., heart, muscle) and will not occur in cells derived from the ectoderm or the endoderm.

[0045] The methods disclosed herein may comprise taking one or more samples from one or more organs developed from one of the three germ layers. The methods disclosed herein may comprise

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monitoring tissues of one or more organs developed from one of the three germ layers. The methods disclosed herein may comprise predicting the origin of distal nucleic acids from one or more organs developed from one of the three germ layers. In some cases, the organs developed from the ectoderm may include epidermis, hair, nails, lens of the eye, sebaceous glands, cornea, tooth enamel, the epithelium of the mouth and nose, peripheral nervous system, adrenal medulla, melanocytes, facial cartilage, dentin of teeth, brain, spinal cord, posterior pituitary, motor neurons, retina, and neural crest. In other cases, the organs developed from the endoderm may include stomach, colon, liver, pancreas, urinary bladder, epithelial parts of trachea, lungs, pharynx, thyroid, parathyroid, and intestines. In some cases, the organs developed from the mesoderm include muscle (smooth and striated), bone, cartilage, connective tissue, adipose tissue, circulatory system, lymphatic system, dermis, genitourinary system, serous membranes, and notochord. In some cases, the mutation map is generated by mapping the mutation onto a tissue and/or organ in the developmental tree or cell fate map. For example, the mutation map is generated by mapping a mutation unique to one tissue type onto that tissue.

[0046] In some cases, the developmental mutation map can be used to identify the origin of a nucleic acid identified distally to the tissue (e.g., in blood). In some cases, a developmental mutation map, specific for an individual subject, can be used to trace the origin of a nucleic acid identified through sequencing distal nucleic acid molecules. For example, a nucleic acid in the cfDNA of a patient may be identified using the methods described herein. The presence of the nucleic acid may, for example, suggest the presence of a disease, for example, a tumor in the patient's body. However, because the nucleic acid was identified distally, rather than from a biopsy, it can be difficult to identify the tissue of origin. By using the methods described herein, the origin of the nucleic acid can be identified. In this example, the nucleic acid may be screened for one or more mosaic variants. The one or more mosaic variants may be referenced to the developmental mutation map such that the source of the mutation can be identified. It will be appreciated that, depending on when during developmental the mutation occurred, the utility of the developmental mutation map in identifying the originating tissue will vary. A mutation that occurred early in development may exist in multiple tissue types, whereas a mutation that occurred later in development may only exist in one tissue type. For example, a developmental mutation map may identify the originating tissue as endoderm if the developmental mutation occurred shortly after gastrulation. In this scenario, the exact tissue of origin may be unknown, but the number of possible sources may be limited (e.g., endodermal tissue). In another example, a developmental mutation that occurred later in development (i.e., after tissue differentiation), may restrict the tissue of

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origin to one or two tissues (e.g., the developmental mutation occurred in the primitive gut tube suggests the tumor of origin is pancreas, liver or allantois).

[0047] Alternatively, the methods described herein can be used to generate a spatial mutation map. A spatial mutation map can be generated by mapping a mutation onto a spatial map. In some cases, the spatial mutation map may be generated by sampling various tissues of a subject, identifying differential mutations in the various tissues, and mapping the mutations to a spatial map. In this scenario, mutations may be identified that are restricted spatially (e.g., a mutation that is found in cells on the left side of the body but not on the right side of the body). The spatial mutation map may be utilized as a reference to spatially localize mosaic variants identified through distal sampling of a subject. In a similar manner as described above for the developmental mutation map, one or more mosaic variants may be identified on a distal nucleic acid molecule. The one or more mosaic variants can be referenced to a spatial mutation map to spatially restrict a source of the nucleic acid molecule (e.g., left versus right side of the body). In some cases, the spatial map can be a body spatial map. For example, a mutation may only be found in one part (e.g., left hand) of the body but not in the others (e.g., right hand). The mutation map can be generated by mapping the mutation onto that body part (e.g., left hand) in the spatial map.

[0048] Disclosed herein is a method for generating a mutation map of a subject that relates a mutation to a source of the mutation. With reference to **FIG. 3**, a method for generating a mutation map comprises: a) obtaining nucleic acid samples from different tissues of the subject, **310 & 320**; b) sequencing nucleic molecules in the nucleic acid samples, **330**; c) identifying with a programmed computer processor differential mutations in nucleic acid sequences of nucleic acid molecules sequenced in (b), **340**; and d) generating in computer memory a relationship between the differential mutations and the different tissues to provide the mutation map of the subject.

[0049] Generating a relationship between the differential mutations and the different tissues may comprise (i) assigning the differential mutations on one or more tissues based on e.g., a developmental tree or a body spatial map, **350** and (ii) generating the developmental mutation map from the developmental tree or a body spatial map, **360**. In a case when a developmental tree is used, the mutation map is a developmental mutation map. In a case when a body spatial map is used, the mutation map is a spatial mutation map. The mutation map may be generated using a hierarchical tree clustering algorithm. The method may further comprise providing a report with the developmental mutation map and/or the spatial mutation map.

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[0050] Once a mutation map has been obtained, it may be used to determine the source of a nucleic acid molecule or portion thereof in a subject, and/or to monitor the state(s) of health of one or more tissues of a subject. With reference to **FIG. 4**, a method for monitoring state(s) of health one or more tissues of a subject comprise a) obtaining at least one nucleic acid molecule from a blood sample of the subject, **410**; b) sequencing the nucleic acid molecule to generate a nucleic acid sequence of the nucleic acid molecule, **420**; c) identifying one or more mutations in the nucleic acid sequence, **430**; and d) using a mutation map of the subject **450** in computer memory, identifying with a programmed computer processor a tissue of the subject associated with the nucleic acid molecule based on the one or more mutations identified in (c), **440**. The method may further comprise providing a report with the tissue identified in (d), **460**. The report may be provided on an electronic display having a user interface. The method may further comprise a determination of the state of health of the subject, **470**. The method may further comprise providing a therapeutic intervention based on a determination of the state of health of the subject, **480**.

[0051] The method of **FIG. 4** may be used to classify the one or more tissues as, for example, healthy, unhealthy, or potentially unhealthy. From such classification, a healthcare profession (e.g., a doctor) may diagnose and/or treat the subject.

[0052] Methods provided herein may be used to detect differential mutations in a blood sample of a subject. With reference to **FIG. 5**, a method for detecting differential mutations in a blood sample of a subject comprises a) separating the blood sample into at least a first component that includes cell-free or surface-bound nucleic acid molecules and a second component that includes leukocytes, **510**; b) extracting nucleic acid molecules from the first and second components, **520**; c) independently sequencing extracted nucleic molecules from the first and second components, **530**; and d) comparing with a programmed computer processor nucleic acid sequences of nucleic acid molecules of the first and second components to identify differential mutations, **540**. The method may further comprise (e) identifying a source of the cell-free or surface-bound nucleic acid molecules based on the differential mutations, **550**. The identifying the source may comprise comparing the differential mutation(s) to a mutation map (e.g., developmental mutation map or spatial mutation map) of the subject. The source may be identified as a tissue or group of tissues of the subject. The method may further comprise providing a report and/or a therapeutic intervention based on an identification of the source.

[0053] The changes in the amount and/or characteristics of cell-free DNA (cfDNA) and cell-bound DNA can be used to detect diseases (e.g., cancer). The half-life of cfDNA in blood can be shorter than

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that of cell-bound DNA (e.g. about 15 minutes vs several days). In a healthy individual, the amount of cell-bound DNA in a given quantity of blood may be 20x to 100x higher than the amount of cfDNA. Cell-bound DNA may be more sensitive to longer term signals (e.g. tumor growth or other diseases) and cfDNA can be used to detect transient DNA signals from transient events. These transient events may be due to the cycles of healthy physiology (e.g. sleep vs awake, monthly menstrual cycles, meals and digestion, pregnancy, etc), or due to intentional manipulation of specific parts of the body (e.g. exercise, heating / cooling, local administration or uptake of specific drugs, etc). The transient or other time varying characteristics of these distal DNA signals may allow them to be separated out from a combination of such signals.

[0054] The mosaic variants of individual parts of the body may be carried with these transient or time varying distal DNA signals. In some cases, the method provides for generating a mutation map using transient or time varying distal DNA signals. A method of generating a mutation map may involve sampling distal nucleic acid molecules of a subject during one or more transient events as described above. By observing the signals under these conditions, specific mosaic variants may be mapped to specific parts of the body without having to obtain a tissue or other sample specific to those other parts of the body. For example, cfDNA that originated in the heart may be abundant in a blood sample after cardiovascular exercise. The cfDNA can be sequenced and mutations that are specifically localized to the heart may be identified. The specific mosaic variants can be used as biomarkers for those parts of the body, even if they are not causal for medical condition. These methods can facilitate the generation of a mutation map. Similarly, disease-causing mutations may be identified by sampling distal nucleic acid molecules during one or more transient events, and the origin of those mutations can be identified with a mutation map as described above or by relating the mutations to the one or more transient events (e.g., a mutation that originated in the heart is identified after cardiovascular exercise). Thus when a change in the amount, proportion, or other characteristics of these variants is seen, it can be tied to a change in a specific part of the body.

[0055] Disclosed herein is a method of using cfDNA and cell-bound DNA complementarily. Having used the time resolution of cfDNA to correlate specific mosaic variants with specific parts of the body, the methods can be used to detect, quantify and otherwise characterize changes in these variants via cell-bound DNA, at greater sensitivity than may be possible with cfDNA from an equivalent specimen. The method, for example, can detect, quantify and otherwise characterize changes in these variants via cell-bound DNA with a specificity or sensitivity of about or greater than about 50%, 55%, 60%, 65%, 70%,

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75%, 76%, 77%, 78%, 79%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% as compared to cfDNA from an equivalent specimen. Since the changes on the time scale of blood cell turnover (a few days) or longer, the cell-bound DNA in blood may be more sensitive for detecting changes in sources of DNA. In one case, mosaic variations in the DNA may initially be characterized as from a particular part of the body by stimulating that part of the body (e.g. by exercise) and observing the corresponding transient in the cfDNA signal. Having thus associated a mosaic variant with a particular part of the body, a tumor or other disease growing in that same part of the body may be detected, by detection of that mosaic variant (e.g., biomarker) in cell-bound DNA. Because the growth of tumors may be slower than the time scale of red blood cell turnover, the cell-bound DNA may be a more sensitive detector and thus able to detect the tumor earlier.

[0056] The analysis of mosaic variants in distal nucleic acid sequences, even when those variants are not causal or predisposing for disease, can provide spatial and even organ-specificity not previously associated with assays based on them. The analysis of mosaic variation in distal nucleic acids can demultiplex otherwise combined DNA signals and can improve the sensitivity of such a test for the distal nucleic acid signal. For example, the identification of mosaic variants specific to blood cells and their precursors (e.g. bone marrow) can provide a mechanism to quantify the fraction of a cfDNA (or other distal nucleic acid) which is from blood (e.g., naturally or by rupture of blood cells in the process of obtaining the sample or conducting the assay). By subtracting out the potentially varying baseline, testing of distal nucleic acids can be more specific and/or more sensitive, for example, about or greater than about 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5% more specific and/or more sensitive than non-blood sources.

[0057] Samples, which are nearby on a developmental tree or a body spatial map, may be used to link specific mosaic variants to parts of the body which are difficult, expensive or invasive to assay directly. For example, because the bladder is close to the pancreas on the developmental tree (both are derived from the gut tube), mosaicism in bladder cells from urine (e.g., inexpensively and non-invasively obtainable) can be used as a surrogate marker for the pancreas (e.g., much more invasive to assay). In another case, because the spinal cord is close to the brain on the developmental tree, cells from the spinal cord, in cerebrospinal fluid, can be used as surrogate markers for the brain (e.g., expensive and much more invasive to assay.

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[0058] The method may also be used to perform tumor vs normal analysis without a tissue specimen from the tumor, and thus can be used to identify specific variants in the tumor and to recommend specific anti-cancer drugs based on the mutation to be targeted. The normal analysis may be performed on white blood cells (i.e., leukocytes) prior to the development of the tumor. In some cases, the normal analysis and the tumor analysis are performed on a single blood sample. In this case, whole blood can be collected and centrifuged to separate the plasma which contains the cfDNA, the buffy coat which contains the white blood cells, and the red blood cells. Nucleic acids can be extracted from the plasma and the white blood cells and sequenced. In some cases, the cfDNA may contain distal nucleic acids that originated from a tumor. In these cases, tumor variants may be identified by identifying mosaic variants in the cfDNA that are not represented in the white blood cells ("normal"). In some cases, the tumor variants are causal variants (i.e., tumor-causing).

Sample processing and analysis

[0059] The methods disclosed herein may comprise providing individual sequence reads from individual distal nucleic acids. In some cases, the methods may comprise identifying mosaic mutations specific to at least one particular subset of patient's cells. The particular subset of patient's cells may comprise cells from a specific organ or set of organs. The particular subset of patient's cells may comprise cells from a spatial segment of the body (e.g., the left or right side of the body).

[0060] The methods may comprise counting the number of reads in each such subset. In some cases, counting the number of reads may be done by sequencing. In particular, counting the number of reads may be done by next-generation sequencing (NGS). For example, the individual sequence reads can be obtained using an Illumina HiSeq or MiSeq system. Alternatively, the individual sequence reads can be obtained using a digital genotyping system. In some cases, counting the number of reads may be done by monitoring one or several specific mosaic loci with assays that have analog readouts. In some cases, counting the number of reads may be done by oligo-directed single base extension. In some cases, counting the number of reads may be done by monitoring one or several specific mosaic loci with fluorescence assays. In some cases, counting the number of reads may be done by monitoring one or several specific mosaic loci with mass-spec assays. In some cases, counting the number of reads may be done by monitoring one or several specific mosaic loci with genotyping assays. In some cases, counting the number of reads may be done by monitoring one or several specific mosaic loci with arrays assays (e.g., microarray assays).

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[0061] The methods may comprise normalizing the number of reads. In some cases, the number of reads exhibiting a specific mosaic variant may be normalized to the total number of reads. In some cases, the number of reads may be normalized to the time of day. In some cases, the number of reads may be normalized to the phase of menstrual cycle. In some cases, the number of reads may be normalized to the subject's body weight.

[0062] The methods may comprise comparing the number of reads, in some cases normalized, in each subset to a reference number. In some cases, the reference number is calculated from other subjects. In some cases, the reference number is calculated from the same subject.

[0063] The methods may comprise reporting the number of reads, localization, cell type, spatial position in the body, and/or other values based on the comparison. In one example, the values based on the comparison may be a statistically significant increase in read counts from a mosaic variant known to be in the patient's pancreas. The methods may comprise reporting the changes in the overall set of sequences. In some cases, the change is an increase or decrease in the overall amount of cfDNA. In some cases, the change is an increase or decrease in the ratio of certain sequences to others. For example, the certain sequences are sequences from regions frequently amplified in cancer (e.g., MET). The methods may comprise reporting the changes of mosaic and non-mosaic loci in other patient events. The patient events may be trauma, pregnancy, diagnosed diseases and/or organ transplantation.

[0064] The methods may comprise correlating results of mosaic loci with other changes in the overall set of sequences. The methods may comprise correlating results of mosaic loci with other patient events.

[0065] The methods as disclosed herein may comprise isolating cfDNA from a sample, in some cases a blood sample. In some cases, isolating cfDNA from a blood sample comprises avoiding rupture of blood cells. In some cases, isolating cfDNA from a blood sample comprises centrifuging blood first at a lower speed, and then later at a higher speed. In some cases, the blood cells contain more mosaic variants than other tissues. For example, the blood cells contain at least 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% more mosaic variants than other tissues. In some cases, the blood-specific mosaic variants may be identified by sequencing DNA from the thin layer formed by centrifugation of blood (e.g., "Buffy Coat"). In some cases, the blood-specific mosaic variants may be identified by sequencing DNA from white blood cells. In some cases, the blood-specific signal may be identified by quantifying the signal with blood-specific mosaic variants.

[0066] The methods as disclosed herein may further comprise subtracting out the blood-specific signal from other signals. In some cases, the blood-specific signal may be monitored. For example, an increase

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of the blood-specific signal from the cfDNA component may indicate a disease in blood or other organs, such as liver. In some cases, subtracting out the blood-specific signal may reduce the background signal. In some cases, subtracting out the blood-specific signal may improve the sensitivity of signals from other parts of the body. In some cases, subtracting out the blood-specific signal involves subtracting out the quantity of blood-specific cfDNA from the overall quantity of cfDNA. In other cases, subtracting out the blood-specific signal involves only counting the non-blood signal at genomic loci with variants that are not identified in the blood-specific data.

[0067] The methods as disclosed herein may further comprise assaying a set of mosaic variants associated with specific parts of the body. In some cases, assaying the set of mosaic variants may detect the presence of the mosaic variants in the distal DNA at low concentrations, for example less than about 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, or 1%. In some cases, assaying the set of mosaic variants may detect the presence of the mosaic variants in the distal DNA at even lower concentrations, for example less than about 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.08%, 0.06%, 0.04%, 0.02%, or 0.01%. In some cases, the methods may comprise PCR amplification of mosaic variants. In some cases, the PCR amplification of mosaic variants is more rapid than exome or whole genome sequencing. In some cases, the PCR amplification of mosaic variants takes less than 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50% of the time needed for completing an exome sequencing for the same sample. For example, the PCR amplification of mosaic variants takes less than 80% of the time needed for completing an exome sequencing for the same sample. In some cases, the PCR amplification of mosaic variants takes less than 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50% of the time needed for completing a whole genome sequencing for the same sample. For example, the PCR amplification of mosaic variants takes less than 80% of the time needed for completing a whole genome sequencing for the same sample. In some cases, the PCR amplification of mosaic variants is at least 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, or 50% less expensive than exome or whole genome sequencing. For example, the PCR amplification of mosaic variants is at least 80% less expensive than exome or whole genome sequencing.

[0068] The methods as disclosed herein may comprise analog or digital assays. The methods as disclosed herein may comprise sequencing or genotyping. In some cases, the methods may comprise using one assay to find the mosaic variants specific to the individual first. In some cases, the methods may further comprise using a second assay once the mosaic variants specific to the individual have been identified. For example, the second assay may be specific to the individual. In some cases, the second

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assay may be used many times over the person's life. For example, the second assay may be used at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50 or more times over the person's life. In some cases, the second assay may use samples from many parts of the individual's body.

[0069] The methods as disclosed herein may be used to detect, monitor, diagnose, and/or treat neurologic diseases, such as amyotrophic lateral sclerosis (ALS), arteriovenous malformation, brain aneurysm, brain tumors, dural arteriovenous fistulae, epilepsy, headache, memory disorders, multiple sclerosis, Parkinson's disease, peripheral neuropathy, post-herpetic neuralgia, spinal cord tumor and stroke. In some cases, the methods may comprise taking a sample from cerebrospinal fluid.

[0070] The methods as disclosed herein may comprise identification of non-causal genetic variants. In some cases, the non-causal genetic variants occur at different proportions in different parts of the body. In some cases, the identification of the non-causal genetic variants comprises sequencing of samples from different parts of the body. In some cases, one or more samples may be obtained in the subject's life. In some cases, the methods may comprise using the one or more samples to improve the map connecting the mosaicism to the organs, cell types, and 3D physiology. In some cases, the samples are obtained by biopsy. For example, the samples can be obtained by non-invasive methods such as sampling the skin or hair. In some cases, the samples are obtained by surgery. For example, the samples can be obtained in a heart surgery to install a pacemaker. In another example, the samples can be obtained in a brain surgery to reduce the incidence of seizures. In another example, the samples can be obtained in a needle biopsy screening for breast cancer. In another example, the samples can be obtained in a surgery for hip replacement. In another example, the samples can be obtained in a surgery for cataract removal. In another example, the samples can be obtained in a surgery for caesarian section. In another example, the samples can be obtained in a surgery for colonoscopy. In another example, the samples can be obtained in a surgery for kidney transplant. In another example, the samples can be obtained in a surgery for root canal.

[0071] The methods as disclosed herein may comprise detecting structural variants (e.g., chromosomal-scale variants) in distal nucleic acids. The methods as disclosed herein may comprise detecting mosaic variants in distal nucleic acids. In some cases, the methods may comprise isolating individual cells from a sample. In some cases, the methods may comprise detecting a cell with structural variants. In some cases, the methods may comprise detecting mosaic variants in the same cell. In some cases, the methods may comprise identifying the source of the cell with structural variants by mapping the mosaic variants to the individual's mutation map.

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[0072] The methods as disclosed herein may comprise detecting causal or predisposing genetic variants in distal nucleic acids. The methods may further comprise detecting non-causal variants. The methods may further comprise detecting both causal and non-causal variants. For example, the non-causal variant is a spatially mapped mosaic variant. In some cases, the methods may comprise searching for a causal variant first. Once the causal variant is detected, the methods may further comprise searching for a non-causal variant in the same cell that contains the causal variant. In some cases, searching for the non-causal variant may comprise a deep search for mosaic variants. In some cases, detecting causal and/or non-causal variants may comprise using a reverse emulsion droplet system. The reverse emulsion droplet system may be from Raindance, for example. Alternatively, detecting causal and/or non-causal variants may comprise doing a pullout from a population of large DNA molecules. The large DNA molecules may have the causal variant.

[0073] The methods as disclosed herein may comprise detecting measuring genetic mosaicism in Lynch syndrome patients. In some cases, the Lynch syndrome patient may have more mosaic mutations than healthy subjects. For example, the Lynch syndrome patient may have at least 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 35-fold, 40-fold, 45-fold, 50-fold, 55-fold, 60-fold, 65-fold, 70-fold, 75-fold, 80-fold, 85-fold, 90-fold, 95-fold, 100-fold, 120-fold, 140-fold, 160-fold, 180-fold, or 200-fold more mosaic mutations than healthy subjects. The methods may further comprise detecting, monitoring, and/or diagnosing cancer in Lynch syndrome patients. In some cases, the methods may comprise screening for colon cancer in Lynch syndrome patients. In some cases, the methods may comprise taking one or more biopsy samples during a colonoscopy. In some cases, the biopsy samples may be from locations spaced along the colon. In some cases, the methods may comprise taking biopsy samples using endometrial biopsy.

[0074] The methods as disclosed herein may comprise detecting mosaic variants using a next generation DNA sequencing technology. In some cases, detecting mosaic variants may comprise providing raw sequence reads from individual DNA. For example, the next generation DNA sequencing technology is Illumina's sequencing by synthesis technology.

[0075] The methods as disclosed herein may comprise detecting mosaic variant using a redundant sequencing technology. Next generation DNA sequencing to detect mosaic variants at low allele frequency (within a particular sample) may be limited by the error rate of the sequencing technology. This sequencing error can create a "noise floor", making it difficult to distinguish false positive variants from true positive variants at a low allelic frequency. Several techniques (including Duplex sequencing,

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Safe-SeqS and Circle Sequencing) have been developed to address this, each by creating multiple copies of an original DNA molecule, sequencing them separately and then combining them to create a high accuracy consensus. In some cases, a redundant sequencing technology is utilized to detect variants that occurred after gastrulation. In some cases, the variants are of allele frequencies below the "noise floor" of current next generation sequencing technologies. In these cases, the variants may be below an allele frequency in a sample of less than about 0.1%. These methods may improve the sensitivity and/or specificity of identifying mosaic variants as compared to next generation sequencing methods. In some cases, the sensitivity or specificity may be improved by at least 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%.

[0076] The methods as disclosed herein may comprise using whole genome sequencing. In some cases, the whole genome sequencing is used to identify mosaic variants in a person. The methods may further comprise sequencing the mosaic variant using other methods. In some cases, sequencing the mosaic variant may comprise deep sequencing over a fraction of the genome. For example, the fraction of the genome may be at least about 50; 75; 100; 125; 150; 175; 200; 225; 250; 275; 300; 350; 400; 450; 500; 550; 600; 650; 700; 750; 800; 850; 900; 950; 1,000; 1100; 1200; 1300; 1400; 1500; 1600; 1700; 1800; 1900; 2,000; 3,000; 4,000; 5,000; 6,000; 7,000; 8,000; 9,000; 10,000; 15,000; 20,000; 30,000; 40,000; 50,000; 60,000; 70,000; 80,000; 90,000; 100,000 or more bases or base pairs. In some cases, the genome may be sequenced over 1 million, 2 million, 3 million, 4 million, 5 million, 6 million, 7 million, 8 million, 9 million, 10 million or more than 10 million bases or base pairs. In some cases, the genome may be sequenced over an entire exome (e.g., whole exome sequencing). In some cases, the deep sequencing may comprise acquiring multiple reads over the fraction of the genome. For example, acquiring multiple reads may comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 10,000 reads or more than 10,000 reads over the fraction of the genome.

[0077] The methods as disclosed herein may comprise detecting mosaic variants in specific genomic regions. In some cases, detecting mosaic variants in specific genomic regions may comprise using methods such as PCR, Molecular Inversion Probes, or hybridization. In some cases, sequencing specific genomic regions may comprise using targeted genomic sequencing. In some cases, sequencing specific genomic regions may comprise using exome sequencing. In some cases, the specific genomic regions may comprise mutational spectra of specific human polymerases, mismatch repair genes or any

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combination thereof. In some cases, the specific genomic regions may comprise loci matching generic motifs inferred from the mutational spectra. In some cases, the specific genomic regions may comprise variants commonly seen somatically in cancer. In some cases, the specific genomic regions may comprise variants commonly seen de novo in other diseases, such as autism and schizophrenia. In some cases, the specific genomic regions may comprise somatic variants seen in other individuals. For example, the somatic variants seen in other individuals may be obtained from a database.

[0078] The methods as disclosed herein may comprise detecting low allelic fractions by deep sequencing. In some cases, the deep sequencing is done by next generation sequencing. In some cases, the deep sequencing is done by avoiding error-prone regions. In some cases, the error-prone regions may comprise regions of near sequence duplication, regions of unusually high or low %GC, regions of near homopolymers, di- and tri-nucleotide, and regions of near other short repeats. In some cases, the error-prone regions may comprise regions that lead to DNA sequencing errors (e.g., polymerase slippage in homopolymer sequences).

[0079] The methods as disclosed herein may comprise sequencing regions with high rates of somatic variations. The methods may comprise sequencing regions with low rates of DNA sequencing error. The methods may comprise sequencing regions with high rates of somatic variations and low rates of DNA sequencing error. By sequencing regions with high rates of somatic variations and low rates of DNA sequencing error, the amount of DNA needed per variant detected can be reduced relative to whole genome sequencing by a factor of 10 or more. In some cases, the amount of DNA needed per variant detected can be reduced relative to whole genome sequencing by a factor of 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, or more.

[0080] Apoptosis is a process that involves a cascade of cellular events ultimately leading to chromosomal DNA fragmentation. Necrosis may also lead to chromosomal DNA fragmentation, however, there may be a difference in size of the DNA fragments. In some cases, the DNA fragments from necrosis may be longer than the DNA fragments from apoptosis, and in some cases, substantially longer. This difference in DNA size can be measured and used to distinguish cfDNA from apoptosis and cfDNA from necrosis. The methods as disclosed herein may comprise monitoring the genomic distribution of the cfDNA from necrosis. The methods may comprise monitoring the genomic distribution of the cfDNA from apoptosis. The methods may comprise monitoring the ratio of the cfDNA from necrosis to apoptosis. In some cases, the monitoring the genomic distribution of the cfDNA from apoptosis comprises identifying DNA in mononucleosomal and oligonucleosomal histone-DNA

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complexes. In some cases, monitoring the ratio of the cfDNA from necrosis to apoptosis comprises measuring the length of the cfDNA. In some cases, the average molecule length of the cfDNA from apoptosis is about 50, 75, 100, 110, 120, 130, 140, 150, 160, 170, 180, 200, 210, 220, 230, 240, 250, 300, 350, 400, 450, 500 or more base pairs. In some cases, the average molecule length of the cfDNA from necrosis is about 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10000, or more base pairs. In some cases, the average molecule length of the cfDNA from necrosis is longer than the cfDNA from apoptosis. For example, the average molecule length of the cfDNA from necrosis is at least 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10000 or more base pairs longer than the cfDNA from apoptosis. In some cases, the cfDNA from necrosis is distinguished from the cfDNA from apoptosis by the length of the cfDNA.

[0081] In some cases, the ratio of the cfDNA from necrosis to apoptosis can be measured using the methods described herein to identify a tumor. As a tumor grows, the core of the tumor may be starved for oxygen and nutrients which may lead to necrosis of the inner mass of tumor cells ("necrotic core"). DNA from the necrotic core may be released into the bloodstream and detected as cfDNA. The presence of cfDNA from necrosis in a blood sample may indicate the presence of tumor.

[0082] The methods as disclosed herein may comprise isolating cell-bound DNA from a sample. In some cases, the sample may be a blood sample. In some cases, isolating cell-bound DNA may further comprise isolating the red blood cell component from the blood sample first. In this case, as red blood cells do not have DNA, the DNA isolated from the red blood cell component is distal DNA that has bound to the surface of the red blood cells. In some cases, isolating the red blood cell component may comprise using centrifugation. In some cases, isolating the red blood cell component may comprise using flow cytometry. In some cases, isolating the red blood cell component may comprise using fluorescence-activated cell sorting (FACS). In some cases, the cell-bound DNA may be extracted from the red blood cell component of the blood sample. In some cases, the methods may comprise sequencing nucleic molecules in the cell-bound DNA. In some cases, the methods may comprise detecting mosaic variants in the cell-bound DNA. In some cases, the methods may comprise identifying the source of the cell-bound DNA. In some cases, the source of the cell-bound DNA may be bone marrow.

Assays

[0083] In some cases, the methods may comprise obtaining distal nucleic acids separated out from other components of the sample. For example, the methods may comprise obtaining cfDNA separated out

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from the DNA in the rest of the blood. In particular, cfDNA may be compared to DNA contained in the white blood cells (e.g., Leukocytes).

[0084] The methods disclosed herein may comprise isolating cfDNA from blood. In some cases, blood cells may be separated out and returned to circulation in the patient using dialysis. Alternatively, the cfDNA can be siphoned off from the blood stream without removing the blood cells using a membrane permeable to the cfDNA but not to the cells. For example, an expanded Teflon membrane may be used. In some cases, DNA may be motivated to move through the membrane electrophoretically. In some cases, methods may allow more frequent sampling of cfDNA than may normally be medically recommended if the loss of blood cells is required.

[0085] In some cases, the nucleic acid sample described herein can be subjected to a variety of assays. Assays may include, but are not limited to, sequencing, amplification, hybridization, enrichment, isolation, elution, fragmentation, detection, and quantification of one or more nucleic acid molecules. Assays may include methods for preparing one or more nucleic acid molecules.

[0086] In some cases, the nucleic acids in the nucleic acid sample described herein can be amplified. Amplification can be performed at any point during a multi reaction procedure using methods provided herein, e.g., before or after pooling of sequencing libraries from independent reaction volumes and may be used to amplify any suitable target molecule described herein.

[0087] Amplification can be performed by various methods or systems. The nucleic acids may be amplified by polymerase chain reaction (PCR), as described in, for example, U.S. Pat. Nos. 5,928,907 and 6,015,674, each of which is entirely incorporated herein by reference. Other methods of nucleic acid amplification may include, for example, ligase chain reaction, oligonucleotide ligations assay, and hybridization assay, as described in greater detail in U.S. Pat. Nos. 5,928,907 and 6,015,674, each of which is entirely incorporated herein by reference. Real-time optical detection systems may be employed, for example, as described in U.S. Pat. Nos. 5,928,907 and 6,015,674, each of which is entirely incorporated herein by reference. Other amplification methods that can be used herein include those described in U.S. Patent Nos. 5,242,794; 5,494,810; 4,988,617; and 6,582,938, each of which is entirely incorporated herein by reference. Other amplification techniques that can be used with methods of the present disclosure can include, e.g., AFLP (amplified fragment length polymorphism) PCR (see e.g.: Vos et al. 1995. AFLP: a new technique for DNA fingerprinting. Nucleic Acids Research 23: 4407-14), allele-specific PCR (see e.g., Saiki R K, Bugawan T L, Horn G T, Mullis K B, Erlich H A (1986). Analysis of enzymatically amplified beta-globin and HLA-DQ alpha DNA with allele-specific

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oligonucleotide probes Nature 324: 163-166), Alu PCR, assembly PCR (see e.g., Stemmer W P, Crameri A, Ha K D, Brennan T M, Heyneker H L (1995). Single-step assembly of a gene and entire plasmid from large numbers of oligodeoxyribonucleotides Gene 164: 49-53), asymmetric PCR (see e.g., Saiki R K supra), colony PCR, helicase dependent PCR (see e.g., Myriam Vincent, Yan Xu and Huimin Kong (2004). Helicase-dependent isothermal DNA amplification EMBO reports 5 (8): 795-800), hot start PCR, inverse PCR (see e.g., Ochman H, Gerber A S, Hartl D L. Genetics. 1988 November; 120(3):621-3), in situ PCR, intersequence-specific PCR or IS SR PCR, digital PCR, linear-after-the-exponential-PCR or Late PCR (see e.g., Pierce K E and Wangh L T (2007). Linear-after-the-exponential polymerase chain reaction and allied technologies Real-time detection strategies for rapid, reliable diagnosis from single cells (Methods Mol. Med. 132: 65-85), long PCR, nested PCR, real-time PCR, duplex PCR, multiplex PCR, quantitative PCR, quantitative fluorescent PCR (QF-PCR), multiplex fluorescent PCR (MF-PCR), restriction fragment length polymorphism PCR (PCR-RFLP), PCK-RFLPIRT-PCR-IRFLP, polony PCR, in situ rolling circle amplification (RCA), bridge PCR, picotiter PCR, and emulsion PCR, or single cell PCR. Other suitable amplification methods can include transcription amplification, self-sustained sequence replication, selective amplification of target polynucleotide sequences, consensus sequence primed polymerase chain reaction (CP-PCR), arbitrarily primed polymerase chain reaction (AP-PCR), and degenerate oligonucleotide-primed PCR (DOP-PCR). Another method for achieving the result of an amplification of nucleic acids is ligase chain reaction (LCR), nucleic acid sequence based amplification (NASBA), Q-beta-replicase method, 3SR (see for example Fahy et al. PCR Methods Appl. 1:25-33 (1991)), or Transcription Mediated Amplification (TMA) used by Gen-Probe. TMA is similar to NASBA in utilizing two enzymes in a self-sustained sequence replication. See U.S. Pat. No. 5,299,491 herein incorporated by reference. Other methods for amplification of nucleic acids can include Strand Displacement Amplification (SDA) (Westin et al 2000, Nature Biotechnology, 18, 199-202; Walker et al 1992, Nucleic Acids Research, 20, 7, 1691-1696), or Rolling Circle Amplification (RCA) (Lizardi et al. 1998, Nature Genetics, 19:225-232).

[0088] In some cases, amplification methods can be solid-phase amplification, polony amplification, colony amplification, emulsion PCR, bead RCA, surface RCA, surface SDA, etc., as will be recognized by one of skill in the art. In some cases, amplification methods that results in amplification of free DNA molecules in solution or tethered to a suitable matrix by only one end of the DNA molecule can be used. Methods that rely on bridge PCR, where both PCR primers are attached to a surface (see, e.g., WO 2000/018957 and Adessi et al., Nucleic Acids Research (2000): 28(20): E87) can be used. A

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"polymerase colony technology" or "polony" may be used, referring to a multiplex amplification that maintains spatial clustering of identical amplicons (see Harvard Molecular Technology Group and Lipper Center for Computational Genetics website). These include, for example, in situ polonies (Mitra and Church, Nucleic Acid Research 27, e34, Dec. 15, 1999), in situ rolling circle amplification (RCA) (Lizardi et al., Nature Genetics 19, 225, July 1998), bridge PCR (U.S. Pat. No. 5,641,658), picotiter PCR (Leamon et al., Electrophoresis 24, 3769, November 2003), and emulsion PCR (Dressman et al., PNAS 100, 8817, Jul. 22, 2003).

[0089] Amplification may be achieved through any process by which the copy number of a target sequence is increased, e.g., PCR. Conditions favorable to the amplification of target sequences by PCR can be optimized at a variety of operations in the process, and depend on characteristics of elements in the reaction, such as target type, target concentration, sequence length to be amplified, sequence of the target and/or one or more primers, primer length, primer concentration, polymerase used, reaction volume, ratio of one or more elements to one or more other elements, and others, some or all of which can be altered. In general, PCR involves the operations of denaturation of the target to be amplified (if double stranded), hybridization of one or more primers to the target, and extension of the primers by a DNA polymerase, with the operations repeated (or "cycled") in order to amplify the target sequence. Operations in this process can be optimized for various outcomes, such as to enhance yield, decrease the formation of spurious products, and/or increase or decrease specificity of primer annealing. Methods of optimization may include adjustments to the type or amount of elements in the amplification reaction and/or to the conditions of a given operation in the process, such as temperature at a particular operation, duration of a particular operation, and/or number of cycles. In some cases, an amplification reaction comprises at least 5, 10, 15, 20, 25, 30, 35, 50, or more cycles. In some cases, an amplification reaction comprises no more than 5, 10, 15, 20, 25, 35, 50, or more cycles. Cycles can contain any number of operations, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more operations. Operations can comprise any temperature or gradient of temperatures, suitable for achieving the purpose of the given operation, including but not limited to, 3' end extension (e.g., adaptor fill-in), primer annealing, primer extension, and strand denaturation. Operations can be of any duration, including but not limited to about, less than about, or more than about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 180, 240, 300, 360, 420, 480, 540, 600, or more seconds, including indefinitely until manually interrupted. Cycles of any number comprising different operations can be combined in any order. In some cases, different

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cycles comprising different operations are combined such that the total number of cycles in the combination is about, less that about, or more than about 5, 10, 15, 20, 25, 30, 35, 50, or more cycles.

[0090] The methods herein may further comprise conducting one or more hybridization reactions on one or more nucleic acid molecules in a sample. The hybridization reactions may comprise the hybridization of one or more capture probes to one or more nucleic acid molecules in a sample or subset of nucleic acid molecules. The hybridization reactions may comprise hybridizing one or more capture probe sets to one or more nucleic acid molecules in a sample or subset of nucleic acid molecules. The hybridization reactions may comprise one or more hybridization arrays, multiplex hybridization reactions, hybridization chain reactions, isothermal hybridization reactions, nucleic acid hybridization reactions, or a combination thereof. The one or more hybridization arrays may comprise hybridization array genotyping, hybridization array proportional sensing, DNA hybridization arrays, macroarrays, microarrays, high-density oligonucleotide arrays, genomic hybridization arrays, comparative hybridization arrays, or a combination thereof. The hybridization reaction may comprise one or more capture probes, one or more beads, one or more labels, one or more subsets of nucleic acid molecules, one or more nucleic acid samples, one or more reagents, one or more wash buffers, one or more elution buffers, one or more hybridization buffers, one or more hybridization chambers, one or more incubators, one or more separators, or a combination thereof.

[0091] The methods disclosed herein may further comprise conducting one or more enrichment reactions on one or more nucleic acid molecules in a sample. The enrichment reactions may comprise contacting a sample with one or more beads or bead sets. The enrichment reaction may comprise differential amplification of two or more subsets of nucleic acid molecules based on one or more genomic region features. For example, the enrichment reaction comprises differential amplification of two or more subsets of nucleic acid molecules based on GC content. Alternatively, or additionally, the enrichment reaction comprises differential amplification of two or more subsets of nucleic acid molecules based on methylation state. The enrichment reactions may comprise one or more hybridization reactions. The enrichment reactions may further comprise isolation and/or purification of one or more hybridized nucleic acid molecules, one or more bead bound nucleic acid molecules, one or more free nucleic acid molecules (e.g., capture probe free nucleic acid molecules, bead free nucleic acid molecules), one or more labeled nucleic acid molecules, one or more non-labeled nucleic acid molecules, one or more amplicons, one or more non-amplified nucleic acid molecules, or a combination

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thereof. Alternatively, or additionally, the enrichment reaction may comprise enriching for one or more cell types in the sample. The one or more cell types may be enriched by flow cytometry.

[0092] The methods disclosed herein may comprise enrichment reactions for different genomic or non-genomic regions and may comprise one or more different amplification operations to prepare libraries of nucleic acid molecules for assay. The one or more enrichment reactions may produce one or more enriched nucleic acid molecules. The enriched nucleic acid molecules may comprise a nucleic acid molecule or variant or derivative thereof. For example, the enriched nucleic acid molecules comprise one or more hybridized nucleic acid molecules, one or more bead bound nucleic acid molecules, one or more free nucleic acid molecules (e.g., capture probe free nucleic acid molecules, bead free nucleic acid molecules), one or more labeled nucleic acid molecules, one or more non-labeled nucleic acid molecules, one or more amplicons, one or more non-amplified nucleic acid molecules, or a combination thereof. The enriched nucleic acid molecules may be differentiated from non-enriched nucleic acid molecules by GC content, molecular size, genomic regions, genomic region features, or a combination thereof. The enriched nucleic acid molecules may be derived from one or more assays, supernatants, eluants, or a combination thereof. The enriched nucleic acid molecules may differ from the non-enriched nucleic acid molecules by mean size, mean GC content, genomic regions, or a combination thereof.

[0093] The methods disclosed herein may further comprise conducting one or more isolation or purification reactions on one or more nucleic acid molecules in a sample. The isolation or purification reactions may comprise contacting a sample with one or more beads or bead sets. The isolation or purification reaction may comprise one or more hybridization reactions, enrichment reactions, amplification reactions, sequencing reactions, or a combination thereof. The isolation or purification reaction may comprise the use of one or more separators. The one or more separators may comprise a magnetic separator. The isolation or purification reaction may comprise separating bead bound nucleic acid molecules from bead free nucleic acid molecules. The isolation or purification reaction may comprise separating capture probe hybridized nucleic acid molecules from capture probe free nucleic acid molecules. The isolation or purification reaction may comprise separating a first subset of nucleic acid molecules from a second subset of nucleic acid molecules, wherein the first subset of nucleic acid molecules differ from the second subset on nucleic acid molecules by mean size, mean GC content, genomic regions, or a combination thereof.

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[0094] The methods disclosed herein may further comprise conducting one or more elution reactions on one or more nucleic acid molecules in a sample. The elution reactions may comprise contacting a sample with one or more beads or bead sets. The elution reaction may comprise separating bead bound nucleic acid molecules from bead free nucleic acid molecules. The elution reaction may comprise separating capture probe hybridized nucleic acid molecules from capture probe free nucleic acid molecules. The elution reaction may comprise separating a first subset of nucleic acid molecules from a second subset of nucleic acid molecules, wherein the first subset of nucleic acid molecules differ from the second subset on nucleic acid molecules by mean size, mean GC content, genomic regions, or a combination thereof.

[0095] The methods disclosed herein may further comprise one or more fragmentation reactions. The fragmentation reactions may comprise fragmenting one or more nucleic acid molecules in a sample or subset of nucleic acid molecules to produce one or more fragmented nucleic acid molecules. The one or more nucleic acid molecules may be fragmented by sonication, needle shear, nebulisation, shearing (e.g., acoustic shearing, mechanical shearing, point-sink shearing), passage through a French pressure cell, or enzymatic digestion. Enzymatic digestion may occur by nuclease digestion (e.g., micrococcal nuclease digestion, endonucleases, exonucleases, RNAse H or DNase I). Fragmentation of the one or more nucleic acid molecules may result in fragment sized of about 100 base pairs to about 2000 base pairs, about 200 base pairs to about 1500 base pairs, about 200 base pairs to about 1000 base pairs, about 200 base pairs to about 500 base pairs, about 500 base pairs to about 1500 base pairs, and about 500 base pairs to about 1000 base pairs. The one or more fragmentation reactions may result in fragment sized of about 50 base pairs to about 1000 base pairs. The one or more fragmentation reactions may result in fragment sized of about 100 base pairs, 150 base pairs, 200 base pairs, 250 base pairs, 300 base pairs, 350 base pairs, 400 base pairs, 450 base pairs, 500 base pairs, 550 base pairs, 600 base pairs, 650 base pairs, 700 base pairs, 750 base pairs, 800 base pairs, 850 base pairs, 900 base pairs, 950 base pairs, 1000 base pairs or more.

[0096] Fragmenting the one or more nucleic acid molecules may comprise mechanical shearing of the one or more nucleic acid molecules in the sample for a period of time. The fragmentation reaction may occur for at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500 or more seconds.

[0097] Fragmenting the one or more nucleic acid molecules may comprise contacting a nucleic acid sample with one or more beads. Fragmenting the one or more nucleic acid molecules may comprise

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contacting the nucleic acid sample with a plurality of beads, wherein the ratio of the volume of the plurality of beads to the volume of nucleic acid sample is about 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.00, 1.10, 1.20, 1.30, 1.40, 1.50, 1.60, 1.70, 1.80, 1.90, 2.00 or more. Fragmenting the one or more nucleic acid molecules may comprise contacting the nucleic acid sample with a plurality of beads, wherein the ratio of the volume of the plurality of beads to the volume of nucleic acid is about 2.00, 1.90, 1.80, 1.70, 1.60, 1.50, 1.40, 1.30, 1.20, 1.10, 1.00, 0.90, 0.80, 0.70, 0.60, 0.50, 0.40, 0.30, 0.20, 0.10, 0.05, 0.04, 0.03, 0.02, 0.01 or less.

[0098] The methods disclosed herein may further comprise conducting one or more detection reactions on one or more nucleic acid molecules in a sample. Detection reactions may comprise one or more sequencing reactions. Alternatively, conducting a detection reaction comprises optical sensing, electrical sensing, or a combination thereof. Optical sensing may comprise optical sensing of a photoilluminscence photon emission, fluorescence photon emission, pyrophosphate photon emission, chemiluminescence photon emission, or a combination thereof. Electrical sensing may comprise electrical sensing of an ion concentration, ion current modulation, nucleotide electrical field, nucleotide tunneling current, or a combination thereof.

[0099] The methods disclosed herein may further comprise conducting one or more quantification reactions on one or more nucleic acid molecules in a sample. Quantification reactions may comprise sequencing, PCR, qPCR, digital PCR, or a combination thereof.

[0100] The methods disclosed herein may further comprise conducting 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 45 or more, or 50 or more assays on a sample comprising one or more nucleic acid molecules. The two or more assays may be different, similar, identical, or a combination thereof. For example, the methods disclosed herein comprise conducting two or more sequencing reactions. In another example, the methods disclosed herein comprise conducting two or more assays, wherein at least one of the two or more assays comprises a sequencing reaction. In yet another example, the methods disclosed herein comprise conducting two or more assays, wherein at least two of the two or more assays comprises a sequencing reaction and a hybridization reaction. The two or more assays may be performed sequentially, simultaneously, or a combination thereof. For example, the two or more sequencing reactions may be performed simultaneously. In another example, the methods disclosed herein comprise conducting a hybridization reaction, followed by a sequencing reaction. In yet another example, the

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methods disclosed herein comprise conducting two or more hybridization reactions simultaneously, followed by conducting two or more sequencing reactions simultaneously. The two or more assays may be performed by one or more devices. For example, two or more amplification reactions may be performed by a PCR machine. In another example, two or more sequencing reactions may be performed by two or more sequencers.

[0101] The methods disclosed herein may further comprise providing individual sequence reads from individual distal nucleic acids. For example, the individual sequence reads can be obtained using an Illumina HiSeq or MiSeq system. In another example, the individual sequence reads can be obtained using a digital genotyping system.

Performance

[0102] The methods disclosed herein can detect one or more genomic regions (i.e., copy number variation, or one or more polymorphisms) with a specificity or sensitivity of about or greater than about 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%, or a positive predictive value or negative predictive value of about or at least about 80%, 85%, 90%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, 98%, 98.5%, 99%, 99.5% or more. The methods disclosed herein can detect one or more genomic regions (i.e., copy number variation, or one or more polymorphisms) with a specificity or sensitivity of about or greater than about 50%. The methods disclosed herein can diagnose a specific condition based on the detected genomic regions such as copy number variation. The methods can diagnose a specific condition with a specificity or sensitivity of greater than 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.5%, or a positive predictive value or negative predictive value of at least 80%, 85%, 90%, 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, 98%, 98.5%, 99%, 99.5% or more.

[0103] The methods disclosed herein may increase the sensitivity or specificity when compared to the sensitivity or specificity of current sequencing methods. For example without limitation, in some cases, the combined whole exome sequencing and a whole genome sequencing reactions may increase the sensitivity or specificity in detecting one or more copy number variations or diagnosing a specific condition when compared to the sensitivity or specificity of whole exome sequencing alone. The sensitivity or specificity of the methods as described herein may increase by at least about 1%, 2%, 3%, 4%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, 10%, 10.5%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 70%, 80%, 90%, 95%.,

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97% or more. The sensitivity or specificity of the methods as described herein may increase by at least about 4.5-20%, about 5-15%, about 7%-12%, or about 8%-10%. In some cases, the methods disclosed herein may have a similar sensitivity or specificity when compared to the sensitivity or specificity of a high coverage whole genome sequencing alone.

[0104] In some cases, the methods as described herein comprise combining an untargeted sequencing data (e.g., low coverage whole genome sequencing data) and one or more target-specific sequencing data. The methods and system disclosed herein may have a sensitivity, specificity, positive predictive value or negative predictive value that is similar to a high coverage whole genome sequencing data alone. The sensitivity, specificity, positive predictive value or negative predictive value may be for the detection of one or more haplotypes, SNV, CNV or one or more polymorphisms. In some cases, the methods as disclosed herein comprise untargeted sequencing data (e.g., a low coverage whole genome sequencing data) that may have a sensitivity, specificity, positive predictive value or negative predictive value that is less than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% or 90% for one or more SNV. In some cases, the methods as disclosed herein may have a sensitivity, specificity, positive predictive value or negative predictive value that is less than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% or 90% for one or more polymorphisms, specific genes or genomic regions. In some cases, the untargeted sequencing (e.g., whole genome sequencing) in the methods as disclosed herein may have a sensitivity, specificity, positive predictive value or negative predictive value that is less than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85% or 90% for one or more SNV, one or more polymorphisms or one or more specific genes or genomic regions. In some cases, the target-specific sequencing data may have a sensitivity, specificity, positive predictive value or negative predictive value that is about, at least about or less than about 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or 100%. In some cases, the untargeted sequencing can have a sensitivity, specificity, positive predictive value or negative predictive value that is between about 50% to 80%.

[0105] The methods disclosed herein can detect one or more genomic regions (i.e., copy number variation, or one or more polymorphisms) with an error rate of less than 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, 10% or less. The methods disclosed herein can diagnose a specific condition based on the detected genomic regions such as copy number variation. The methods can diagnose a specific condition with an error rate of less than 0.5%,

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1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, 8%, 8.5%, 9%, 9.5%, 10% or less.

[0106] The percent error of the methods as described herein may be similar to current sequencing methods. For example, without limitation, in some cases, the combined whole exome sequencing and a whole genome sequencing reactions may have a percent error rate in detecting one or more copy number variations or diagnosing a specific condition when compared to the sensitivity of whole exome sequencing alone. The current sequencing methods may be a high coverage whole genome sequencing alone. The percent error rate of the methods as described herein may be within about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 1%, 1.1%., 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, or 2% of the current sequencing methods. The percent error rate of the methods as described herein may be less than the percent error rate of current sequencing methods. The percent error rate of the methods as described herein may be at least about 10%, 9,%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.75%, 1.5%, 1.25%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1% less than the percent error rate of current sequencing methods. The percent error rate of the methods as described herein may be less than about 2%, 1.75%, 1.5%, 1.25%, 1%, 0.75%, 0.50%, 0.25%, 0.10%, 0.075%, 0.050%, 0.025%, or 0.001%. In some cases, the methods disclosed herein may have a similar percent error rate when compared to the sensitivity or specificity of a high coverage whole genome sequencing alone.

[0107] The error of the methods as described herein can be determined as a Phred quality score. The Phred quality score may be assigned to each base call in automated sequencer traces and may be used to compare the efficacy of different sequencing methods. The Phred quality score (Q) may be defined as a property which is logarithmically related to the base-calling error probabilities (P). The Phred quality score (Q) may be calculated as $Q = -10\log10P$. The Phred quality score of the methods as described herein may be similar to the Phred quality score of current sequencing methods. For example without limitation, in some cases, the combined whole exome sequencing and a low coverage whole genome sequencing reactions may have a similar Phred quality score in detecting one or more copy number variations or diagnosing a specific condition when compared to the Phred quality score of whole exome sequencing alone or a high coverage whole genome sequencing alone. The Phred quality score of the methods as described herein may be within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 of the Phred quality score of the methods as described herein. The Phred quality score of the methods as described herein may be less than the Phred quality score of the methods as described herein. The Phred quality score of the methods

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as described herein may be at least about 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 less than the Phred quality score of the methods as described herein. The Phred quality score of the methods as described herein may be greater than 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, or 30. The Phred quality score of the methods as described herein may be greater than 35, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59,or 60. The Phred quality score of the methods as described herein may be at least 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60 or more.

[0108] The accuracy of the one or more sequencing reactions may be similar to current sequencing methods in detecting and identifying one or more specific genomic regions. The current sequencing methods can be a whole exome sequencing alone or a high coverage whole genome sequencing alone. The accuracy of the methods as described herein may be within about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 1%, 1.1%., 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2%, 2.25%, 2.5%, 2.75%, 3%, 3.25%, 3.5%, 3.75%, or 4% of the current sequencing methods. The accuracy of the methods as described herein may be greater than the accuracy of current sequencing methods. The accuracy of the methods as described herein may be at least about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 1%, 1.1%., 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2%, 2.25%, 2.5%, 2.75%, 3%, 3.25%, 3.5%, 3.75%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 15%, 17%, 20%, 25%, 30%, 35%, 40%, 50%, or 60% greater than the accuracy of current sequencing methods. The accuracy of the methods as described herein may be greater than about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98.25%, 98.5%, 98.75%, 99%, 99.25%, 99.5%, or 99.75%. The accuracy of the methods as described herein may be greater than about 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, 99.99%, or 90.999%.

[0109] The methods disclosed herein can generate an output data identifying one or more specific genomic regions (i.e., copy number variation, or one or more polymorphisms) in a shorter time than a high coverage whole genome sequencing alone. In some cases, the methods as described herein can identify specific genomic regions in less than 1 month, 3.5 weeks, 3 weeks, 2.5 weeks, 2 weeks, 1.5 weeks or 1 week. In some cases, the methods as described herein can identify specific genomic regions in less than 6, 5, 4, 3, 2 or 1 days. In some cases, the methods as described herein can identify specific genomic regions in less than 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2

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or 1 hours. In some cases, the methods as described herein can identify specific genomic regions in less than 60, 59, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 minutes. In some cases, the methods as described herein can identify specific genomic regions in less than 10 minutes. In some cases, the methods as described herein can identify specific genomic regions in less than 5 minutes.

[0110] The methods disclosed herein can generate an output data identifying one or more specific genomic regions (i.e., copy number variation, or one or more polymorphisms) more economically or using less reagents than a high coverage whole genome sequencing alone. In some cases, the methods as described herein can identify specific genomic regions with 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% less financial charges to the customers or less reagents for sequencing reactions used.

Genomic regions

[00111] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions. The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more sets of genomic regions. The one or more genomic regions may comprise one or more genomic region features. The genomic region features may comprise an entire genome or a portion thereof. The genomic region features may comprise an entire exome or a portion thereof. The genomic region features may comprise one or more sets of genes. The genomic region features may comprise one or more genes. The genomic region features may comprise one or more sets of regulatory elements. The genomic region features may comprise one or more regulatory elements. The genomic region features may comprise a set of polymorphisms. The genomic region features may comprise one or more polymorphisms. The genomic region feature may relate to the GC content, complexity, and/or mappablity of one or more nucleic acid molecules. The genomic region features may comprise one or more simple tandem repeats (STRs), unstable expanding repeats, segmental duplications, single and paired read degenerative mapping scores, GRCh37 patches, or a combination thereof. The genomic region features may comprise one or more low mean coverage regions from whole genome sequencing (WGS), zero mean coverage regions from WGS, validated compressions, or a combination thereof. The genomic region features may comprise one or more alternate or non-reference sequences. The genomic region features may comprise one or more gene phasing and reassembly genes. In some aspects of the disclosure, the one or more genomic region features are not mutually exclusive. For example, a genomic region feature comprising an entire genome or a portion thereof can overlap with an additional

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genomic region feature such as an entire exome or a portion thereof, one or more genes, one or more regulatory elements, etc. Alternatively, the one or more genomic region futures are mutually exclusive. For example, a genomic region comprising the noncoding portion of an entire genome may not overlap with a genomic region feature such as an exome or portion thereof or the coding portion of a gene. Alternatively, or additionally, the one or more genomic region features are partially exclusive or partially inclusive. For example, a genomic region comprising an entire exome or a portion thereof can partially overlap with a genomic region comprising an exon portion of a gene. However, the genomic region comprising the entire exome or portion thereof may not overlap with the genomic region comprising the intron portion of the gene. Thus, a genomic region feature comprising a gene or portion thereof may partially exclude and/or partially include a genomic region feature comprising an entire exome or portion thereof.

[00112] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature comprising an entire genome or portion thereof. The entire genome or portion thereof may comprise one or more coding portions of the genome, one or more noncoding portions of the genome, or a combination thereof. The coding portion of the genome may comprise one or more coding portions of a gene encoding for one or more proteins. The one or more coding portions of the genome may comprise an entire exome or a portion thereof. Alternatively, or additionally, the one or more coding portions of the genome may comprise one or more exons. The one or more noncoding portions of the genome may comprise one or more noncoding molecules or a portion thereof. The noncoding molecules may comprise one or more noncoding RNA, one or more regulatory elements, one or more introns, one or more pseudogenes, one or more repeat sequences, one or more transposons, one or more viral elements, one or more telomeres, a portion thereof, or a combination thereof. The noncoding RNAs may be functional RNA molecules that are not translated into protein. Examples of noncoding RNAs include, but are not limited to, ribosomal RNA, transfer RNA, piwi-interacting RNA, microRNA, siRNA, shRNA, snoRNA, sncRNA, and lncRNA. Pseudogenes may be related to known genes and are typically no longer expressed. Repeat sequences may comprise one or more tandem repeats, one or more interspersed repeats, or a combination thereof. Tandem repeats may comprise one or more satellite DNA, one or more minisatellites, one or more microsatellites, or a combination thereof. Interspersed repeats may comprise one or more transposons. Transposons may be mobile genetic elements. Mobile genetic elements are often able to change their

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position within the genome. Transposons may be classified as class I transposable elements (class I TEs) or class II transposable elements (class II TEs). Class I TEs (e.g., retrotransposons) may often copy themselves in two stages, first from DNA to RNA by transcription, then from RNA back to DNA by reverse transcription. The DNA copy may then be inserted into the genome in a new position. Class I TEs may comprise one or more long terminal repeats (LTRs), one or more long interspersed nuclear elements (LINEs), one or more short interspersed nuclear elements (SINEs), or a combination thereof. Examples of LTRs include, but are not limited to, human endogenous retroviruses (HERVs), medium reiterated repeats 4 (MER4), and retrotransposon. Examples of LINEs include, but are not limited to, LINE1 and LINE2. SINEs may comprise one or more Alu sequences, one or more mammalian-wide interspersed repeat (MIR), or a combination thereof. Class II TEs (e.g., DNA transposons) often do not involve an RNA intermediate. The DNA transposon is often cut from one site and inserted into another site in the genome. Alternatively, the DNA transposon is replicated and inserted into the genome in a new position. Examples of DNA transposons include, but are not limited to, MER1, MER2, and mariners. Viral elements may comprise one or more endogenous retrovirus sequences. Telomeres are often regions of repetitive DNA at the end of a chromosome.

[00113] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature comprising an entire exome or portion thereof. The exome is often the part of the genome formed by exons. The exome may be formed by untranslated regions (UTRs), splice sites and/or intronic regions. The entire exome or portion thereof may comprise one or more exons of a protein coding gene. The entire exome or portion thereof may comprise one or more untranslated regions (UTRs), splice sites, and introns.

[00114] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature comprising a gene or portion thereof. Typically, a gene comprises stretches of nucleic acids that code for a polypeptide or a functional RNA. A gene may comprise one or more exons, one or more introns, one or more untranslated regions (UTRs), or a combination thereof. Exons are often coding sections of a gene, transcribed into a precursor mRNA sequence, and within the final mature RNA product of the gene. Introns are often noncoding sections of a gene, transcribed into a precursor mRNA sequence, and removed by RNA splicing. UTRs may refer to sections on each side of a coding sequence on a strand of mRNA. A UTR located on the 5' side of a

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coding sequence may be called the 5' UTR (or leader sequence). A UTR located on the 3' side of a coding sequence may be called the 3' UTR (or trailer sequence). The UTR may contain one or more elements for controlling gene expression. Elements, such as regulatory elements, may be located in the 5' UTR. Regulatory sequences, such as a polyadenylation signal, binding sites for proteins, and binding sites for miRNAs, may be located in the 3' UTR. Binding sites for proteins located in the 3' UTR may include, but are not limited to, selenocysteine insertion sequence (SECIS) elements and AU-rich elements (AREs). SECIS elements may direct a ribosome to translate the codon UGA as selenocysteine rather than as a stop codon. AREs are often stretches consisting primarily of adenine and uracil nucleotides, which may affect the stability of an mRNA.

[00115] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature comprising a set of genes. The sets of genes may include, but are not limited to, Mendel DB Genes, Human Gene Mutation Database (HGMD) Genes, Cancer Gene Census Genes, Online Mendelian Inheritance in Man (OMIM) Mendelian Genes, HGMD Mendelian Genes, and human leukocyte antigen (HLA) Genes. The set of genes may have one or more known Mendelian traits, one or more known disease traits, one or more known drug traits, one or more known biomedically interpretable variants, or a combination thereof. A Mendelian trait may be controlled by a single locus and may show a Mendelian inheritance pattern. A set of genes with known Mendelian traits may comprise one or more genes encoding Mendelian traits including, but are not limited to, ability to taste phenylthiocarbamide (dominant), ability to smell (bitter almond-like) hydrogen cyanide (recessive), albinism (recessive), brachydactyly (shortness of fingers and toes), and wet (dominant) or dry (recessive) earwax. A disease trait cause or increase risk of disease may be inherited in a Mendelian or complex pattern. A set of genes with known disease traits may comprise one or more genes encoding disease traits including, but are not limited to, Cystic Fibrosis, Hemophilia, and Lynch Syndrome. A drug trait may alter metabolism, optimal dose, adverse reactions and side effects of one or more drugs or family of drugs. A set of genes with known drug traits may comprise one or more genes encoding drug traits including, but are not limited to, CYP2D6, UGT1A1 and ADRB1. A biomedically interpretable variant may be a polymorphism in a gene that is associated with a disease or indication. A set of genes with known biomedically interpretable variants may comprise one or more genes encoding biomedically interpretable variants including, but are not limited to, cystic fibrosis (CF) mutations, muscular dystrophy mutations, p53 mutations, Rb mutations, cell cycle

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regulators, receptors, and kinases. Alternatively, or additionally, a set of genes with known biomedically interpretable variants may comprise one or more genes associated with Huntington's disease, cancer, cystic fibrosis, muscular dystrophy (e.g., Duchenne muscular dystrophy).

[00116] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature comprising a regulatory element or a portion thereof. Regulatory elements may be cis-regulatory elements or trans-regulatory elements. Cis-regulatory elements may be sequences that control transcription of a nearby gene. Cis-regulatory elements may be located in the 5' or 3' untranslated regions (UTRs) or within introns. Trans-regulatory elements may control transcription of a distant gene. Regulatory elements may comprise one or more promoters, one or more enhancers, or a combination thereof. Promoters may facilitate transcription of a particular gene and may be found upstream of a coding region. Enhancers may exert distant effects on the transcription level of a gene.

[00117] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature comprising a polymorphism or a portion thereof. Generally, a polymorphism refers to a mutation in a genotype. A polymorphism may comprise one or more base changes, an insertion, a repeat, or a deletion of one or more bases. Copy number variants (CNVs), transversions, and other rearrangements are also forms of genetic variation. Polymorphic markers include restriction fragment length polymorphisms, variable number of tandem repeats (VNTR's), hypervariable regions, minisatellites, dinucleotide repeats, trinucleotide repeats, tetranucleotide repeats, simple sequence repeats, and insertion elements such as Alu. The allelic form occurring most frequently in a selected population is sometimes referred to as the wildtype form. Diploid organisms may be homozygous or heterozygous for allelic forms. A diallelic polymorphism has two forms. A triallelic polymorphism has three forms. Single nucleotide polymorphisms (SNPs) are a form of polymorphisms. In some aspects of the disclosure, one or more polymorphisms comprise one or more single nucleotide variations, inDels, small insertions, small deletions, structural variant junctions, variable length tandem repeats, flanking sequences, or a combination thereof. The one or more polymorphisms may be located within a coding and/or non-coding region. The one or more polymorphisms may be located within, around, or near a gene, exon, intron, splice site, untranslated

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region, or a combination thereof. The one or more polymorphisms may span at least a portion of a gene, exon, intron, untranslated region.

[00118] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature comprising one or more simple tandem repeats (STRs), unstable expanding repeats, segmental duplications, single and paired read degenerative mapping scores, GRCh37 patches, or a combination thereof. The one or more STRs may comprise one or more homopolymers, one or more dinucleotide repeats, one or more trinucleotide repeats, or a combination thereof. The one or more homopolymers may be about 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more bases or base pairs. The dinucleotide repeats and/or trinucleotide repeats may be about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50 or more bases or base pairs. The single and paired read degenerative mapping scores may be based on or derived from alignability of 100mers by GEM from ENCODE/CRG (Guigo), alignability of 75mers by GEM from ENCODE/CRG (Guigo), 100 base pair box car average for signal mappability, max of locus and possible pairs for paired read score, or a combination thereof. The genomic region features may comprise one or more low mean coverage regions from whole genome sequencing (WGS), zero mean coverage regions from WGS, validated compressions, or a combination thereof. The low mean coverage regions from WGS may comprise regions generated from Illumina v3 chemistry, regions below the first percentile of Poission distribution based on mean coverage, or a combination thereof. The Zero mean coverage regions from WGS may comprise regions generated from Illumina v3 chemistry. The validated compressions may comprise regions of high mapped depth, regions with two or more observed haplotypes, regions expected to be missing repeats in a reference, or a combination thereof. The genomic region features may comprise one or more alternate or non-reference sequences. The one or more alternate or non-reference sequences may comprise known structural variant junctions, known insertions, known deletions, alternate haplotypes, or a combination thereof. The genomic region features may comprise one or more gene phasing and reassembly genes. Examples of phasing and reassembly genes include, but are not limited to, one or more major histocompatibility complexes, blood typing, and amylase gene family. The one or more major histocompatibility complexes may comprise one or more HLA Class I, HLA Class II, or a combination thereof. The one or more HLA class I may comprise HLA-A, HLA-B, HLA-C, or a combination thereof. The one or more HLA class II may comprise HLA-

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DP, HLA-DM, HLA-DOA, HLA-DOB, HLA-DQ, HLA-DR, or a combination thereof. The blood typing genes may comprise ABO, RHD, RHCE, or a combination thereof.

[00119] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature related to the GC content of one or more nucleic acid molecules. The GC content may refer to the GC content of a nucleic acid molecule. Alternatively, the GC content may refer to the GC content of one or more nucleic acid molecules and may be referred to as the mean GC content. As used herein, the terms "GC content" and "mean GC content" may be used interchangeably. The GC content of a genomic region may be a high GC content. Typically, a high GC content refers to a GC content of greater than or equal to about 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, or more. In some aspects of the disclosure, a high GC content may refer to a GC content of greater than or equal to about 70%. The GC content of a genomic region may be a low GC content. Typically, a low GC content refers to a GC content of less than or equal to about 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 5%, 2%, or less.

[00120] The difference in GC content may be used to differentiate two or more genomic regions or two or more subsets of nucleic acid molecules. The difference in GC content may refer to the difference in GC content of one nucleic acid molecule and another nucleic acid molecule. Alternatively, the difference in GC content may refer to the difference in mean GC content of two or more nucleic acid molecules in a genomic region from the mean GC content of two or more nucleic acid molecules in another genomic region. In some aspects of the disclosure, the difference in GC content refers to the difference in mean GC content of two or more nucleic acid molecules in a subset of nucleic acid molecules from the mean GC content of two or more nucleic acid molecules in another subset of nucleic acid molecules. The difference in GC content may be about 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or more. In some aspects of the disclosure, the difference in GC content is at least about 5%. The difference in GC content may be at least about 10%.

[00121] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature related to the complexity of one or more nucleic acid molecules. The complexity of a nucleic acid molecule may refer to the randomness of a nucleotide sequence. Low complexity may refer to patterns, repeats and/or depletion of one or more species of nucleotide in the sequence.

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[00122] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region feature related to the mappablity of one or more nucleic acid molecules. The mappability of a nucleic acid molecule may refer to uniqueness of its alignment to a reference sequence. A nucleic acid molecule with low mappability may have poor alignment to a reference sequence.

[00123] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions comprising one or more genomic region features. In some aspects of the disclosure, a single genomic region comprises 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, or 15 or more genomic region features. The two or more genomic regions may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more genomic region features. In some aspects of the disclosure, two or more genomic regions comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, or 15 or more genomic region features. The one or more genomic regions may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more identical or similar genomic region features. Alternatively, or additionally, two or more genomic regions comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, or 15 or more genomic region features. The one or more genomic regions may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more different genomic region features.

[00124] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising two or more genomic regions, wherein the two or more genomic regions are differentiateable by one or more genomic region features. The methods as

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disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising two or more subsets of nucleic acid molecules, wherein the two or more subsets of nucleic acid molecules are differentiateable by one or more genomic region features. The two or more genomic regions and/or the two or more subsets of nucleic acid molecules may be differentiateable by 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, or 15 or more genomic region features. The one or more genomic regions may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, or 30 or more genomic region features.

[00125] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more sets of genomic regions. For example, The methods as disclosed herein may, or comprise the use of, comprise nucleic acid samples or subsets of nucleic acid molecules comprising, 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more sets of genomic regions. The one or more sets of genomic regions may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more different genomic regions. The one or more sets of genomic regions may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more identical or similar genomic regions. The one or more sets of genomic regions may comprise a combination of one or more different genomic regions and one or more identical or similar genomic regions.

[00126] The methods as disclosed herein may comprise, or comprise the use of, nucleic acid samples or subsets of nucleic acid molecules comprising one or more genomic regions, wherein at least one of the one or more genomic regions comprises a genomic region with higher mutation rates. In some cases, the methods may comprise sequencing one or more genomic mutation hot spots. For example, the mutation rates in the genomic mutation hot spots are 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or

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more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more times than the average mutation rates across the genome.

Capture probes

[00127] The methods disclosed herein may comprise, or comprise the use of, one or more capture probes, a plurality of capture probes, or one or more capture probe sets. Typically, the capture probe comprises a nucleic acid binding site. The capture probe may further comprise one or more linkers. The capture probes may further comprise one or more labels. The one or more linkers may attach the one or more labels to the nucleic acid binding site.

[00128] The methods disclosed herein may comprise, or comprise the use of, 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 20 or more, 30 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, 100 or more, 125 or more, 150 or more, 175 or more, 200 or more, 250 or more, 300 or more, 350 or more, 400 or more, 500 or more, 600 or more, 700 or more, 800 or more, 900 or more, or 1000 or more one or more capture probes or capture probe sets. The one or more capture probes or capture probe sets may be different, similar, identical, or a combination thereof.

[00129] The one or more capture probe may comprise a nucleic acid binding site that hybridizes to at least a portion of the one or more nucleic acid molecules or variant or derivative thereof in the sample or subset of nucleic acid molecules. The capture probes may comprise a nucleic acid binding site that hybridizes to one or more genomic regions. The capture probes may hybridize to different, similar, and/or identical genomic regions. The one or more capture probes may be at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99% or more complementary to the one or more nucleic acid molecules or variants or derivatives thereof.

[00130] The capture probes may comprise one or more nucleotides. The capture probes may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 20 or more, 30 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, 100 or more, 125 or more, 150 or more, 175 or more, 200 or more, 250 or more, 300 or more, 350 or more, 400 or more, 500 or more, 600 or more, 700 or more, 800 or more, 900 or more, or 1000 or more nucleotides. The capture probes may comprise about 100 nucleotides. The capture probes may comprise between about 10 to about 500 nucleotides, between about 20 to about 450 nucleotides, between about 30 to about 400 nucleotides, between about 40 to about 350 nucleotides, between about 50 to about 300

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nucleotides, between about 60 to about 250 nucleotides, between about 70 to about 200 nucleotides, or between about 80 to about 150 nucleotides. In some aspects of the disclosure, the capture probes comprise between about 80 nucleotides to about 100 nucleotides.

[00131] The plurality of capture probes or the capture probe sets may comprise two or more capture probes with identical, similar, and/or different nucleic acid binding site sequences, linkers, and/or labels. For example, two or more capture probes comprise identical nucleic acid binding sites. In another example, two or more capture probes comprise similar nucleic acid binding sites. In yet another example, two or more capture probes comprise different nucleic acid binding sites. The two or more capture probes may further comprise one or more linkers. The two or more capture probes may further comprise different linkers. The two or more capture probes may further comprise similar linkers. The two or more capture probes may further comprise identical linkers. The two or more capture probes may further comprise one or more labels. The two or more capture probes may further comprise different labels. The two or more capture probes may further comprise similar labels. The two or more capture probes may further comprise identical labels.

Diseases or Conditions

[00132] The methods as disclosed herein may comprise, or comprise the use of, predicting, diagnosing, and/or prognosing a status or outcome of a disease or condition in a subject based on one or more biomedical outputs. Predicting, diagnosing, and/or prognosing a status or outcome of a disease in a subject may comprise diagnosing a disease or condition, identifying a disease or condition, determining the stage of a disease or condition, assessing the risk of a disease or condition, assessing the risk of disease recurrence, assessing reproductive risk, assessing genetic risk to a fetus, assessing the efficacy of a drug, assessing risk of an adverse drug reaction, predicting optimal drug dosage, predicting drug resistance, or a combination thereof.

[0133] The samples disclosed herein may be from a subject suffering from a cancer. The sample may comprise malignant tissue, benign tissue, or a mixture thereof. The cancer may be a recurrent and/or refractory cancer. Examples of cancers include, but are not limited to, sarcomas, carcinomas, lymphomas or leukemias.

[0134] Sarcomas are cancers of the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Sarcomas include, but are not limited to, bone cancer, fibrosarcoma, chondrosarcoma, Ewing's sarcoma, malignant hemangioendothelioma, malignant schwannoma, bilateral vestibular schwannoma, osteosarcoma, soft tissue sarcomas (e.g., alveolar soft part sarcoma, angiosarcoma,

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cystosarcoma phylloides, dermatofibrosarcoma, desmoid tumor, epithelioid sarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, and synovial sarcoma).

[0135] Carcinomas are cancers that begin in the epithelial cells, which are cells that cover the surface of the body, produce hormones, and make up glands. By way of non-limiting example, carcinomas include breast cancer, pancreatic cancer, lung cancer, colon cancer, colorectal cancer, rectal cancer, kidney cancer, bladder cancer, stomach cancer, prostate cancer, liver cancer, ovarian cancer, brain cancer, vaginal cancer, vulvar cancer, uterine cancer, oral cancer, penile cancer, testicular cancer, esophageal cancer, skin cancer, cancer of the fallopian tubes, head and neck cancer, gastrointestinal stromal cancer, adenocarcinoma, cutaneous or intraocular melanoma, cancer of the anal region, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, cancer of the urethra, cancer of the renal pelvis, cancer of the ureter, cancer of the endometrium, cancer of the cervix, cancer of the pituitary gland, neoplasms of the central nervous system (CNS), primary CNS lymphoma, brain stem glioma, and spinal axis tumors. The cancer may be a skin cancer, such as a basal cell carcinoma, squamous, melanoma, nonmelanoma, or actinic (solar) keratosis.

[0136] The cancer may be a lung cancer. Lung cancer can start in the airways that branch off the trachea to supply the lungs (bronchi) or the small air sacs of the lung (the alveoli). Lung cancers include non-small cell lung carcinoma (NSCLC), small cell lung carcinoma, and mesothelioma. Examples of NSCLC include squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The mesothelioma may be a cancerous tumor of the lining of the lung and chest cavity (pleura) or lining of the abdomen (peritoneum). The mesothelioma may be due to asbestos exposure. The cancer may be a brain cancer, such as a glioblastoma.

[0137] Alternatively, the cancer may be a central nervous system (CNS) tumor. CNS tumors may be classified as gliomas or nongliomas. The glioma may be malignant glioma, high grade glioma, diffuse intrinsic pontine glioma. Examples of gliomas include astrocytomas, oligodendrogliomas (or mixtures of oligodendroglioma and astrocytoma elements), and ependymomas. Astrocytomas include, but are not limited to, low-grade astrocytomas, anaplastic astrocytomas, glioblastoma multiforme, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma. Oligodendrogliomas include low-grade oligodendrogliomas (or oligoastrocytomas) and anaplastic

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oligodendriogliomas. Nongliomas include meningiomas, pituitary adenomas, primary CNS lymphomas, and medulloblastomas. The cancer may be a meningioma.

[0138] The leukemia may be an acute lymphocytic leukemia, acute myelocytic leukemia, chronic lymphocytic leukemia, or chronic myelocytic leukemia. Additional types of leukemias include hairy cell leukemia, chronic myelomonocytic leukemia, and juvenile myelomonocytic leukemia.

[0139] Lymphomas are cancers of the lymphocytes and may develop from either B or T lymphocytes. The two major types of lymphoma are Hodgkin's lymphoma, previously known as Hodgkin's disease, and non-Hodgkin's lymphoma. Hodgkin's lymphoma is marked by the presence of the Reed-Sternberg cell. Non-Hodgkin's lymphomas are all lymphomas which are not Hodgkin's lymphoma. Non-Hodgkin lymphomas may be indolent lymphomas and aggressive lymphomas. Non-Hodgkin's lymphomas include, but are not limited to, diffuse large B cell lymphoma, follicular lymphoma, mucosa-associated lymphatic tissue lymphoma (MALT), small cell lymphocytic lymphoma, mantle cell lymphoma, Burkitt's lymphoma, mediastinal large B cell lymphoma, Waldenström macroglobulinemia, nodal marginal zone B cell lymphoma (NMZL), splenic marginal zone lymphoma (SMZL), extranodal marginal zone B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, and lymphomatoid granulomatosis.

[0140] Additional diseases and/or conditions include, but are not limited to, atherosclerosis, inflammatory diseases, autoimmune diseases, rheumatic heart disease. Examples of inflammatory diseases include, but are not limited to, acne vulgaris, Alzheimer's, ankylosing spondylitis, arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis), asthma, atherosclerosis, celiac disease, chronic prostatitis, Crohn's disease, colitis, dermatitis, diverticulitis, fibromyalgia, glomerulonephritis, hepatitis, irritable bowel syndrome (IBS), systemic lupus erythematous (SLE), nephritis, Parkinson's disease, pelvic inflammatory disease, sarcoidosis, ulcerative colitis, and vasculitis.

[0141] Examples of autoimmune diseases include, but are not limited to, acute disseminated encephalomyelitis (ADEM), Addison's disease, agammaglobulinemia, alopecia areata, amyotrophic Lateral Sclerosis, ankylosing spondylitis, antiphospholipid syndrome, antisynthetase syndrome, atopic allergy, atopic dermatitis, autoimmune aplastic anemia, autoimmune cardiomyopathy, autoimmune enteropathy, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease, autoimmune lymphoproliferative syndrome, autoimmune peripheral neuropathy, autoimmune pancreatitis, autoimmune polyendocrine syndrome, autoimmune progesterone dermatitis, autoimmune thrombocytopenic purpura, autoimmune urticaria, autoimmune uveitis, Balo disease/Balo concentric

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sclerosis, Behçet's disease, Berger's disease, Bickerstaff's encephalitis, Blau syndrome, bullous pemphigoid, Castleman's disease, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, chronic recurrent multifocal osteomyelitis, chronic obstructive pulmonary disease, Churg-Strauss syndrome, cicatricial pemphigoid, Cogan syndrome, cold agglutinin disease, complement component 2 deficiency, contact dermatitis, cranial arteritis, CREST syndrome, Crohn's disease, Cushing's syndrome, cutaneous leukocytoclastic angiitis, Dego's disease, Dercum's disease, dermatitis herpetiformis, dermatomyositis, diabetes mellitus type 1, diffuse cutaneous systemic sclerosis, Dressler's syndrome, drug-induced lupus, discoid lupus erythematosus, eczema, endometriosis, enthesitis-related arthritis, eosinophilic fasciitis, eosinophilic gastroenteritisvepidermolysis bullosa acquisita, erythema nodosum, erythroblastosis fetalis, essential mixed cryoglobulinemia, Evan's syndrome, fibrodysplasia ossificans progressiva, fibrosing alveolitis (or idiopathic pulmonary fibrosis), gastritis, gastrointestinal pemphigoid, giant cell arteritis, glomerulonephritis, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, herpes gestationis aka gestational pemphigoid, hidradenitis suppurativa, Hughes-Stovin syndrome, hypogammaglobulinemia, idiopathic inflammatory demyelinating diseases, idiopathic pulmonary fibrosis, IgA nephropathy, inclusion body myositis, chronic inflammatory demyelinating polyneuropathyvinterstitial cystitis, juvenile idiopathic arthritis aka juvenile rheumatoid arthritis, Kawasaki's disease, Lambert-Eaton myasthenic syndrome, leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, linear IgA disease (LAD), Lou Gehrig's disease (Also Amyotrophic lateral sclerosis), lupoid hepatitis aka autoimmune hepatitis, lupus erythematosus, Majeed syndrome, Ménière's disease, microscopic polyangiitis, mixed connective tissue disease, morphea, Mucha-Habermann disease, multiple sclerosis, myasthenia gravis, myositis, neuromyelitis optica (also Devic's disease), neuromyotonia, occular cicatricial pemphigoid, opsoclonus myoclonus syndrome, Ord's thyroiditis, palindromic rheumatism, PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcus), paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonage-Turner syndrome, Pars planitis, pemphigus vulgaris, pernicious anaemia, perivenous encephalomyelitis, POEMS syndrome, polyarteritis nodosa, polymyalgia rheumatica, polymyositis, primary biliary cirrhosis, primary sclerosing cholangitis, progressive inflammatory neuropathy, psoriasis, psoriatic arthritis, pyoderma gangrenosum, pure red cell aplasia, Rasmussen's encephalitis, Raynaud phenomenon, relapsing polychondritis, Reiter's syndrome, restless leg syndrome, retroperitoneal fibrosis, rheumatoid arthritis, rheumatic fever, sarcoidosis, Schmidt

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syndrome another form of APS, Schnitzler syndrome, scleritis, scleroderma, serum sickness, Sjögren's syndrome, spondyloarthropathy, Stiff person syndrome, subacute bacterial endocarditis (SBE), Susac's syndrome, Sweet's syndrome, sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis (also known as "giant cell arteritis"), thrombocytopenia, Tolosa-Hunt syndrome, transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease different from mixed connective tissue disease, undifferentiated spondyloarthropathy, urticarial vasculitis, vasculitis, vitiligo, and Wegener's granulomatosis.

[0142] The methods as provided herein may also be useful for detecting, monitoring, diagnosing and/or predicting a subject's response to an implanted device. Exemplary medical devices include but are not limited to stents, replacement heart valves, implanted cerebella stimulators, hip replacement joints, breast implants, and knee implants.

[0143] The methods as disclosed herein may be used for monitoring the health of a fetus using whole or partial genome analysis of nucleic acids derived from a fetus, as compared to the maternal genome. For example, nucleic acids can be useful in pregnant subjects for fetal diagnostics, with fetal nucleic acids serving as a marker for gender, rhesus D status, fetal aneuploidy, and sex-linked disorders. The methods as disclosed herein may identify fetal mutations or genetic abnormalities. The methods as disclosed herein can enable detection of extra or missing chromosomes, particularly those typically associated with birth defects or miscarriage. The methods as disclosed herein may comprise, or comprise the use of, the diagnosis, prediction or monitoring of autosomal trisomies (e.g., Trisomy 13, 15, 16, 18, 21, or 22) and may be based on the detection of foreign molecules. The trisomy may be associated with an increased chance of miscarriage (e.g., Trisomy 15, 16, or 22). Alternatively, the trisomy that is detected is a liveborn trisomy that may indicate that an infant will be born with birth defects (e.g., Trisomy 13 (Patau Syndrome), Trisomy 18 (Edwards Syndrome), and Trisomy 21 (Down Syndrome)). The abnormality may also be of a sex chromosome (e.g., XXY (Klinefelter's Syndrome), XYY (Jacobs Syndrome), or XXX (Trisomy X). The methods disclosed herein may comprise one or more genomic regions on the following chromosomes: 13, 18, 21, X, or Y. For example, the foreign molecule may be on chromosome 21 and/or on chromosome 18, and/or on chromosome 13. The one or more genomic regions may comprise multiple sites on multiple chromosomes.

[0144] Further fetal conditions that can be determined based on the methods herein include monosomy of one or more chromosomes (X chromosome monosomy, also known as Turner's syndrome), trisomy of one or more chromosomes (13, 18, 21, and X), tetrasomy and pentasomy of one or more

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chromosomes (which in humans is most commonly observed in the sex chromosomes, e.g., XXXX, XXYY, XXXY, XYYY, XXXXX, XXXXY, XXXYY, XYYYY and XXYYY), monoploidy, triploidy (three of every chromosome, e.g., 69 chromosomes in humans), tetraploidy (four of every chromosome, e.g., 92 chromosomes in humans), pentaploidy and multiploidy.

[0145] The methods as disclosed may comprise detecting, monitoring, quantitating, or evaluating one or more pathogen-derived nucleic acid molecules or one or more diseases or conditions caused by one or more pathogens. Exemplary pathogens include, but are not limited to, *Bordetella, Borrelia, Brucella, Campylobacter, Chlamydia, Chlamydophila, Clostridium, Corynebacterium, Enterococcus, Escherichia, Francisella, Haemophilus, Helicobacter, Legionella, Leptospira, Listeria, Mycobacterium, Mycoplasma, Neisseria, Pseudomonas, Rickettsia, Salmonella, Shigella, Staphylococcus, Streptococcus, Treponema, Vibrio,* or *Yersinia.* Additional pathogens include, but are not limited to, *Mycobacterium tuberculosis, Streptococcus, Pseudomonas, Shigella, Campylobacter*, and *Salmonella.*

[0146] The disease or conditions caused by one or more pathogens may comprise tuberculosis, pneumonia, foodborne illnesses, tetanus, typhoid fever, diphtheria, syphilis, leprosy, bacterial vaginosis, bacterial meningitis, bacterial pneumonia, a urinary tract infection, bacterial gastroenteritis, and bacterial skin infection. Examples of bacterial skin infections include, but are not limited to, impetigo which may be caused by *Staphylococcus aureus* or *Streptococcus pyogenes*; erysipelas which may be caused by a streptococcus bacterial infection of the deep epidermis with lymphatic spread; and cellulitis which may be caused by normal skin flora or by exogenous bacteria.

[0147] The pathogen may be a fungus, such as, *Candida, Aspergillus, Cryptococcus, Histoplasma, Pneumocystis,* and *Stachybotrys.* Examples of diseases or conditions caused by a fungus include, but are not limited to, jock itch, yeast infection, ringworm, and athlete's foot.

[0148] The pathogen may be a virus. Examples of viruses include, but are not limited to, adenovirus, coxsackievirus, Epstein-Barr virus, Hepatitis virus (e.g., Hepatitis A, B, and C), herpes simplex virus (type 1 and 2), cytomegalovirus, herpes virus, HIV, influenza virus, measles virus, mumps virus, papillomavirus, parainfluenza virus, poliovirus, respiratory syncytial virus, rubella virus, and varicella-zoster virus. Examples of diseases or conditions caused by viruses include, but are not limited to, cold, flu, hepatitis, AIDS, chicken pox, rubella, mumps, measles, warts, and poliomyelitis.

[0149] The pathogen may be a protozoan, such as *Acanthamoeba (e.g., A. astronyxis, A. castellanii, A. culbertsoni, A. hatchetti, A. polyphaga, A. rhysodes, A. healyi, A. divionensis), Brachiola (e.g., B connori, B. vesicularum), Cryptosporidium (e.g., C. parvum), Cyclospora (e.g., C. cayetanensis),*

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Encephalitozoon (e.g., E. cuniculi, E. hellem, E. intestinalis), Entamoeba (e.g., E. histolytica), Enterocytozoon (e.g., E. bieneusi), Giardia (e.g., G. lamblia), Isospora (e.g, I. belli), Microsporidium (e.g., M. africanum, M. ceylonensis), Naegleria (e.g., N. fowleri), Nosema (e.g., N. algerae, N. ocularum), Pleistophora, Trachipleistophora (e.g., T. anthropophthera, T. hominis), and *Vittaforma (e.g., V. corneae).*

Devices

[0150] The methods disclosed herein may comprise the use of one or more devices. The methods disclosed herein may comprise the use of one or more devices to perform one or more operations or assays comprised therein. The methods disclosed herein may comprise one or more devices and the use thereof in one or more operations or assays. In particular, the methods disclosed herein may comprise one or more devices to provide individual sequence reads from individual molecules of distal nucleic acids. For example, conducting a sequencing reaction may comprise one or more sequencers. In another example, combining a plurality of data inputs and generating a combined data may comprise the use of one or more computer processors. In yet another example, one or more processors may be used in the generating and displaying electronically at least a portion of the data output. Exemplary devices include, but are not limited to, sequencers, computer processors, computer display, monitors, hard drives, thermocyclers, real-time PCR instruments, magnetic separators, transmission devices, hybridization chambers, electrophoresis apparatus, centrifuges, microscopes, imagers, fluorometers, luminometers, plate readers, computers, processors, and bioanalyzers.

[0151] The methods disclosed herein may comprise one or more sequencers. The one or more sequencers may comprise one or more HiSeq, MiSeq, HiScan, Genome Analyzer IIx, SOLiD Sequencer, Ion Torrent PGM, 454 GS Junior, Pac Bio RS, or a combination thereof. The one or more sequencers may comprise one or more sequencing platforms. The one or more sequencing platforms may comprise GS FLX by 454 Life Technologies/Roche, Genome Analyzer by Solexa/Illumina, SOLiD by Applied Biosystems, CGA Platform by Complete Genomics, PacBio RS by Pacific Biosciences, or a combination thereof.

[0152] The methods disclosed herein may comprise one or more thermocyclers. The one or more thermocyclers may be used to amplify one or more nucleic acid molecules. The methods disclosed herein may comprise one or more real-time PCR instruments. The one or more real-time PCR instruments may comprise a thermal cycler and a fluorimeter. The one or more thermocyclers may be used to amplify and detect one or more nucleic acid molecules.

[0153] The methods disclosed herein may comprise one or more magnetic separators. The one or more magnetic separators may be used for separation of paramagnetic and ferromagnetic particles from a suspension. The one or more magnetic separators may comprise one or more LifeStep™ biomagnetic separators, SPHERO™ FlexiMag separator, SPHERO™ MicroMag separator, SPHERO™ HandiMag separator, SPHERO™ MiniTube Mag separator, SPHERO™ UltraMag separator, DynaMag™ magnet, DynaMag™-2 Magnet, or a combination thereof.

[0154] The methods disclosed herein may comprise one or more bioanalyzers. Generally, a bioanalyzer is a chip-based capillary electrophoresis machine that can analyze RNA, DNA, and proteins. The one or more bioanalyzers may comprise Agilent's 2100 Bioanalyzer. The methods disclosed herein may comprise one or more genotyping systems, for example, a digital genotyping system.

Computer control systems

[0155] The present disclosure provides computer control systems that are programmed to implement methods of the disclosure. **FIG. 6** shows a computer system **601** that is programmed or otherwise configured to implement the methods and systems disclosed herein. The computer system **601** can implement various aspects of the present disclosure, such as, for example, generating of a mutation map, sequencing a nucleic acid sequence, identifying a differential mutation and/or generating a report. The computer system **601** can be an electronic device of a user or a computer system that is remotely located with respect to the electronic device. The electronic device can be a mobile electronic device.

[0156] The computer system **601** includes a central processing unit (CPU, also "processor" and "computer processor" herein) **605**, which can be a single core or multi core processor, or a plurality of processors for parallel processing. The computer system **601** also includes memory or memory location **610** (e.g., random-access memory, read-only memory, flash memory), electronic storage unit **615** (e.g., hard disk), communication interface **620** (e.g., network adapter) for communicating with one or more other systems, and peripheral devices **625**, such as cache, other memory, data storage and/or electronic display adapters. The memory **610**, storage unit **615**, interface **620** and peripheral devices **625** are in communication with the CPU **605** through a communication bus (solid lines), such as a motherboard. The storage unit **615** can be a data storage unit (or data repository) for storing data. The computer system **601** can be operatively coupled to a computer network ("network") **630** with the aid of the communication interface **620**. The network **630** can be the Internet, an internet and/or extranet, or an intranet and/or extranet that is in communication with the Internet. The network **630** in some cases is a telecommunication and/or data network. The network **630** can include one or more computer servers,

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which can enable distributed computing, such as cloud computing. The network **630**, in some cases with the aid of the computer system **601**, can implement a peer-to-peer network, which may enable devices coupled to the computer system **601** to behave as a client or a server.

[0157] The CPU **605** 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 **610**. The instructions can be directed to the CPU **605**, which can subsequently program or otherwise configure the CPU **605** to implement methods of the present disclosure. Examples of operations performed by the CPU **605** can include fetch, decode, execute, and writeback.

[0158] The CPU **605** can be part of a circuit, such as an integrated circuit. One or more other components of the system **601** can be included in the circuit. In some cases, the circuit is an application specific integrated circuit (ASIC).

[0159] The storage unit **615** can store files, such as drivers, libraries and saved programs. The storage unit **615** can store user data, e.g., user preferences and user programs. The computer system **601** in some cases can include one or more additional data storage units that are external to the computer system **601**, such as located on a remote server that is in communication with the computer system **601** through an intranet or the Internet.

[0160] The computer system **601** can communicate with one or more remote computer systems through the network **630**. For instance, the computer system **601** can communicate with a remote computer system of a user (e.g., a patient or a physician). 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 **601** via the network **630**.

[0161] 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 **601**, such as, for example, on the memory **610** or electronic storage unit **615**. 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 **605**. In some cases, the code can be retrieved from the storage unit **615** and stored on the memory **610** for ready access by the processor **605**. In some situations, the electronic storage unit **615** can be precluded, and machine-executable instructions are stored on memory **610**.

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[0162] 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.

[0163] Aspects of the systems and methods provided herein, such as the computer system **601**, 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.

[0164] 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

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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.

[0165] The computer system **601** can include or be in communication with an electronic display **635** that comprises a user interface (UI) **640** for providing, for example, a sequencing result, a report about health state and/or a mutation map. Examples of UI's include, without limitation, a graphical user interface (GUI) and web-based user interface.

[0166] Methods and systems of the present disclosure can be implemented by way of one or more algorithms. An algorithm can be implemented by way of software upon execution by the central processing unit **605**. The algorithm can, for example, generate a mutation map.

Subjects

[0167] Often, the methods are used on a subject, in some cases human. The subject may be a male or a female. The subject may be a fetus, infant, child, adolescent, teenager or adult. The subject may be patients of any age. For example, the subject may be a patient of less than about 10 years old. For example, the subject may be a patient of at least about 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 years old. The subject may be *in utero*. Often, the subject is a patient or other individual undergoing a treatment regimen, or being evaluated for a treatment regimen (e.g., immunosuppressive therapy). However, in some instances, the subject is not undergoing a treatment regimen. For example, the subject may be a healthy subject.

[0168] In some cases, the subjects may be mammals or non-mammals. In some cases, the subjects are a mammal, such as, a human, non-human primate (e.g., apes, monkeys, chimpanzees), cat, dog, rabbit, goat, horse, cow, pig, rodent, mouse, SCID mouse, rat, guinea pig, or sheep. In some methods, species variants or homologs of these genes can be used in a non-human animal model. Species variants may be the genes in different species having greatest sequence identity and similarity in functional properties to one another. Many of such species variants human genes may be listed in the Swiss-Prot database.

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[0169] The methods disclosed herein may be used on a transplant recipient who is a recipient of a solid organ or a fragment of a solid organ. The solid organ may be a lung, kidney, heart, liver, pancreas, large intestine, small intestine, gall bladder, reproductive organ or a combination thereof. In some instances, the transplant recipient may be a recipient of a tissue or cell. The tissue or cell may be amnion, skin, bone, blood, marrow, blood stem cells, platelets, umbilical cord blood, cornea, middle ear, heart valve, vein, cartilage, tendon, ligament, nerve tissue, embryonic stem (ES) cells, induced pluripotent stem cells (IPSCs), stem cells, adult stem cells, hematopoietic stem cells, or a combination thereof.

Samples

[0170] The methods disclosed herein may comprise obtaining a sample from a subject, such as a human subject. In particular, the methods may comprise obtaining a clinical specimen from a patient. For example, blood may be drawn from a patient. In some cases, the methods may comprise obtaining distal nucleic acids from multiple sources. The methods disclosed herein may comprise specifically detecting, profiling, or quantitating molecules (e.g., nucleic acids, DNA, RNA, etc.) that are within the biological samples.

[0171] One or more nucleic acids may be isolated from one or more sources. For example, DNA is isolated from one or more sources. In some cases, the sample may be distal nucleic acids obtained from intact cells being transported from their original location. By physiological processes, and disease, the nucleic acids of intact cells can end up in bodily fluids. For example, intact cells of a fetus can be detected in maternal blood. In another example, circulating tumor cells can lead to metastases in cancer.

[0172] In some cases, the sample may be distal nucleic acids obtained from dead cells. When cells die, their membranes become porous and eventually disintegrate the contents of the cell, including the nucleic acids. In some cases, cell death can be a part of normal healthy turnover of cell populations. Alternatively, the cell death can be due to disease, environmental exposure (e.g., chemicals, radiation, viruses, etc.), injury, apoptosis, necrosis or other factors. For example, apoptosis may occur locally in muscle fibers due to exercise. In other cases, apoptosis may occur in human uterine endometrium in certain portions of the menstrual cycle. These nucleic acids may be transported in the bodily fluids. For example, the sample may be distal nucleic acids transported in the form of cell-free DNA (cfDNA). In other cases, the sample may be distal nucleic acids transported in the form of cell-surface-bound DNA (csbDNA). The sample may be distal nucleic acids found in bodily fluids.

[0173] In some cases, the sample may be distal nucleic acids obtained from exosomes. Exosomes are cell-derived vesicles that can be present in many bodily fluids (e.g., blood, urine). Exosomes can be

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secreted from one cell then absorbed by other cells. In some cases, obtaining distal nucleic acids from exosomes may comprise isolating the exosomes from bodily fluids. Obtaining distal nucleic acids from exosomes may further comprise purifying nucleic acids from the isolated exosomes.

[0174] The sample may be a tissue sample or a bodily fluid. In some instances, the sample is a tissue sample or an organ sample, such as a biopsy. The bodily fluid may be sweat, saliva, tears, urine, blood, menses, semen, and/or spinal fluid. In some cases, the sample is a blood sample. The sample may comprise one or more peripheral blood lymphocytes. The sample may be a whole blood sample. The blood sample may be a peripheral blood sample. In some cases, the sample comprises peripheral blood mononuclear cells (PBMCs); in some cases, the sample comprises peripheral blood lymphocytes (PBLs).The sample may be a serum sample.

[0175] The sample may be obtained using any method that can provide a sample suitable for the analytical methods described herein. The sample may be obtained by a non-invasive method such as a throat swab, buccal swab, bronchial lavage, urine collection, scraping of the skin or cervix, swabbing of the cheek, saliva collection, feces collection, menses collection, or semen collection. The sample may be obtained by a minimally-invasive method such as a blood draw. The sample may be obtained by venipuncture. In other instances, the sample is obtained by an invasive procedure including but not limited to: biopsy, alveolar or pulmonary lavage, or needle aspiration. The method of biopsy may include surgical biopsy, incisional biopsy, excisional biopsy, punch biopsy, shave biopsy, or skin biopsy. The sample may be formalin fixed sections. The method of needle aspiration may further include fine needle aspiration, core needle biopsy, vacuum assisted biopsy, or large core biopsy. In some cases, multiple samples may be obtained by the methods herein to ensure a sufficient amount of biological material. In some instances, the sample is not obtained by biopsy. In some instances, the sample is not a kidney biopsy.

Nucleic Acid Samples

[0176] Methods of the present disclosure can be applied to any type of nucleic acid sample. In some cases, the nucleic acid samples can be fragmented double stranded DNA including but not limited to, for example, free DNA isolated from plasma, serum, and/or urine; DNA from apoptotic cells and/or tissues; DNA fragmented enzymatically in vitro (for example, by DNase I and/or restriction endonuclease); and/or DNA fragmented by mechanical forces (hydro-shear, sonication, nebulization, etc.). Additional suitable methods and compositions of producing nucleic acid molecules comprising stem-loop

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oligonucleotides are further described in detail in U.S. Pat. No. 7,803,550, which is herein incorporated by reference in its entirety.

[0177] In other cases, methods provided herein can be easily applied to any high molecular weight double stranded DNA including, for example, DNA isolated from tissues, cell culture, bodily fluids, animal tissue, plant, bacteria, fungi, viruses, etc.

[0178] Nucleic acid obtained from biological samples typically is fragmented to produce suitable fragments for analysis. Template nucleic acids may be fragmented or sheared to desired length, using a variety of mechanical, chemical and/or enzymatic methods. DNA may be randomly sheared via sonication, e.g., Covaris method, brief exposure to a DNase, or using a mixture of one or more restriction enzymes, or a transposase or nicking enzyme. RNA may be fragmented by brief exposure to an RNase, heat plus magnesium, or by shearing. The RNA may be converted to cDNA. If fragmentation is employed, the RNA may be converted to cDNA before or after fragmentation. In one case, nucleic acid from a biological sample is fragmented by sonication. In another case, nucleic acid is fragmented by a hydroshear instrument. Generally, individual nucleic acid template molecules can be from about 100 bases to 100 kilobases (kb), 100 bases to 90 kb, 100 bases to 80 kb, 100 bases to 70 kb, 100 bases to 60 kb, 100 bases to 50 kb, or 100 bases to about 40 kb. Individual nucleic acid template molecules can be at least about 100 bases, 200 bases, 300 bases, 400 bases, 500 bases, 1 kb, 10 kb, 20 kb, 30 kb, 40 kb, 50 kb, 60 kb, 70 kb, 80 kb, 90 kb, 100 kb, 200 kb, 300 kb, 400 kb, or 500 kb. In some cases, nucleic acids are about 100-300, about 200-300, or about 100-500 base fragments. Nucleic acid molecules may be single-stranded, double-stranded, or double-stranded with single-stranded regions (for example, double-stranded DNA with single-stranded overhangs on one or both ends). A biological sample as described herein may be homogenized or fractionated in the presence of a detergent or surfactant. The concentration of the detergent in the buffer may be about 0.05% to about 10.0%. The concentration of the detergent can be up to an amount where the detergent remains soluble in the solution. In one case, the concentration of the detergent is between 0.1% to about 2%. The detergent, particularly a mild one that is nondenaturing, can act to solubilize the sample. Detergents may be ionic or nonionic. Examples of nonionic detergents include triton, such as the Triton® X series (Triton® X-100 t-Oct-C6H4—(OCH2—CH2)xOH, x=9-10, Triton® X-100R, Triton® X-114 x=7-8), octyl glucoside, polyoxyethylene(9)dodecyl ether, digitonin, IGEPAL® CA630 octylphenyl polyethylene glycol, n-octyl-beta-D-glucopyranoside (betaOG), n-dodecyl-beta, Tween® 20 polyethylene glycol sorbitan monolaurate, Tween® 80 polyethylene glycol sorbitan monooleate, polidocanol, n-dodecyl beta-D-

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maltoside (DDM), NP-40 nonylphenyl polyethylene glycol, C12E8 (octaethylene glycol n-dodecyl monoether), hexaethyleneglycol mono-n-tetradecyl ether (C14EO6), octyl-beta-thioglucopyranoside (octyl thioglucoside, OTG), Emulgen, and polyoxyethylene 10 lauryl ether (C12E10). Examples of ionic detergents (anionic or cationic) include deoxycholate, sodium dodecyl sulfate (SDS), N-lauroylsarcosine, and cetyltrimethylammoniumbromide (CTAB). A zwitterionic reagent may also be used in the purification schemes of the present disclosure, such as Chaps, zwitterion 3-14, and 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulf-onate. It is contemplated also that urea may be added with or without another detergent or surfactant.

[0179] Lysis or homogenization solutions may further contain other agents, such as reducing agents. Examples of such reducing agents include dithiothreitol (DTT), .beta.-mercaptoethanol, DTE, GSH, cysteine, cystamine, tricarboxyethyl phosphine (TCEP), or salts of sulfurous acid.

[0180] The methods as disclosed herein may comprise, or comprise the use of, one or more subsets of nucleic acid molecules. The subsets of nucleic acid molecules may be derived from a nucleic acid sample. The subsets of nucleic acid molecules may be derived from the same nucleic acid sample. Alternatively, or additionally, the subsets of nucleic acid molecules are derived from two or more different nucleic acid samples. Two or more subsets of nucleic acid molecules may be differentiated by their nucleic acid content. The one or more subsets of nucleic acid molecules may comprise one or more nucleic acid molecules or a variant or derivative thereof. For example, the two or more subsets of nucleic acid molecules may comprise nucleic acids comprising different GC content, nucleic acid size, genomic regions, genomic region features, eluted nucleic acid molecules, hybridized nucleic acid molecules, non-hybridized nucleic acid molecules, amplified nucleic acid molecules, non-amplified nucleic acid molecules, supernatant-derived nucleic acid molecules, eluant-derived nucleic acid molecules, labeled nucleic acid molecules, non-labeled nucleic acid molecules, capture probe hybridized nucleic acid molecules, capture probe free nucleic acid molecules, bead bound nucleic acid molecules, bead free nucleic acid molecules, or a combination thereof. The two or more subsets of nucleic acid molecules may be differentiated by GC content, nucleic acid size, genomic regions, capture probes, beads, labels, or a combination thereof.

[0181] The methods as disclosed herein may comprise, or comprise the use of, combining two or more subsets of nucleic acid molecules to produce a combined subset of nucleic acid molecules. The combined subsets of nucleic acid molecules may be derived from a nucleic acid sample. The combined subsets of nucleic acid molecules may be derived from the same nucleic acid sample. Alternatively, or

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additionally, the combined subsets of nucleic acid molecules are derived from two or more different nucleic acid samples. Two or more combined subsets of nucleic acid molecules may be differentiated by their nucleic acid content. The one or more combined subsets of nucleic acid molecules may comprise one or more nucleic acid molecules or a variant or derivative thereof. For example, the two or more combined subsets of nucleic acid molecules may comprise nucleic acids comprising different GC content, nucleic acid size, genomic regions, genomic region features, eluted nucleic acid molecules, hybridized nucleic acid molecules, non-hybridized nucleic acid molecules, amplified nucleic acid molecules, non-amplified nucleic acid molecules, supernatant-derived nucleic acid molecules, eluant-derived nucleic acid molecules, labeled nucleic acid molecules, non-labeled nucleic acid molecules, capture probe hybridized nucleic acid molecules, capture probe free nucleic acid molecules, bead bound nucleic acid molecules, bead free nucleic acid molecules, or a combination thereof. The two or more combined subsets of nucleic acid molecules may be differentiated by GC content, nucleic acid size, genomic regions, capture probes, beads, labels, or a combination thereof.

[0182] Subsets of nucleic acid molecules may comprise one or more genomic regions as disclosed herein. Subsets of nucleic acid molecules may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more genomic regions. The one or more genomic regions may be identical, similar, different, or a combination thereof.

[0183] Subsets of nucleic acid molecules may comprise one or more genomic region features as disclosed herein. Subsets of nucleic acid molecules may comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 20 or more, 25 or more, 30 or more, 35 or more, 40 or more, 50 or more, 60 or more, 70 or more, 80 or more, 90 or more, or 100 or more genomic region features. The one or more genomic region features may be identical, similar, different, or a combination thereof.

[0184] Subsets of nucleic acid molecules may comprise nucleic acid molecules of different sizes. The length of a nucleic acid molecule in a subset of nucleic acid molecules may be referred to as the size of the nucleic acid molecule. The average length of the nucleic acid molecules in a subset of nucleic acid molecules may be referred to as the mean size of nucleic acid molecules. As used herein, the terms "size of a nucleic acid molecule", "mean size of nucleic acid molecules", "molecular size" and "mean molecular size" may be used interchangeably. The size of a nucleic acid molecule may be used to

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differentiate two or more subsets of nucleic acid molecules. The difference in the mean size of nucleic acid molecules in a subset of nucleic acid molecules and the mean size of nucleic acid molecules in another subset of nucleic acid molecules may be used to differentiate the two subsets of nucleic acid molecules. The mean size of nucleic acid molecules in one subset of nucleic acid molecules may be greater than the mean size of nucleic acid molecules in at least one other subset of nucleic acid molecules. The mean size of nucleic acid molecules in one subset of nucleic acid molecules may be less than the mean size of nucleic acid molecules in at least one other subset of nucleic acid molecules. The difference in mean molecular size between two or more subsets of nucleic acid molecules may be at least about 50; 75; 100; 125; 150; 175; 200; 225; 250; 275; 300; 350; 400; 450; 500; 550; 600; 650; 700; 750; 800; 850; 900; 950; 1,000; 1100; 1200; 1300; 1400; 1500; 1600; 1700; 1800; 1900; 2,000; 3,000; 4,000; 5,000; 6,000; 7,000; 8,000; 9,000; 10,000; 15,000; 20,000; 30,000; 40,000; 50,000; 60,000; 70,000; 80,000; 90,000; 100,000 or more bases or base pairs. In some aspects of the disclosure, the difference in mean molecular size between two or more subsets of nucleic acid molecules is at least about 200 bases or bases pairs. Alternatively, the difference in mean molecular size between two or more subsets of nucleic acid molecules is at least about 300 bases or bases pairs.

[0185] Subsets of nucleic acid molecules may comprise nucleic acid molecules of different sequencing sizes. The length of a nucleic acid molecule in a subset of nucleic acid molecules to be sequenced may be referred to as the sequencing size of the nucleic acid molecule. The average length of the nucleic acid molecules in a subset of nucleic acid molecules may be referred to as the mean sequencing size of nucleic acid molecules. As used herein, the terms "sequencing size of a nucleic acid molecule", "mean sequencing size of nucleic acid molecules", "molecular sequencing size" and "mean molecular sequencing size" may be used interchangeably. The mean molecular sequencing size of one or more subsets of nucleic acid molecules may be at least about 50; 75; 100; 125; 150; 175; 200; 225; 250; 275; 300; 350; 400; 450; 500; 550; 600; 650; 700; 750; 800; 850; 900; 950; 1,000; 1100; 1200; 1300; 1400; 1500; 1600; 1700; 1800; 1900; 2,000; 3,000; 4,000; 5,000; 6,000; 7,000; 8,000; 9,000; 10,000; 15,000; 20,000; 30,000; 40,000; 50,000; 60,000; 70,000; 80,000; 90,000; 100,000 or more bases or base pairs. The sequencing size of a nucleic acid molecule may be used to differentiate two or more subsets of nucleic acid molecules. The difference in the mean sequencing size of nucleic acid molecules in a subset of nucleic acid molecules and the mean sequencing size of nucleic acid molecules in another subset of nucleic acid molecules may be used to differentiate the two subsets of nucleic acid molecules. The mean sequencing size of nucleic acid molecules in one subset of nucleic acid molecules may be

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greater than the mean sequencing size of nucleic acid molecules in at least one other subset of nucleic acid molecules. The mean sequencing size of nucleic acid molecules in one subset of nucleic acid molecules may be less than the mean sequencing size of nucleic acid molecules in at least one other subset of nucleic acid molecules. The difference in mean molecular sequencing size between two or more subsets of nucleic acid molecules may be at least about 50; 75; 100; 125; 150; 175; 200; 225; 250; 275; 300; 350; 400; 450; 500; 550; 600; 650; 700; 750; 800; 850; 900; 950; 1,000; 1100; 1200; 1300; 1400; 1500; 1600; 1700; 1800; 1900; 2,000; 3,000; 4,000; 5,000; 6,000; 7,000; 8,000; 9,000; 10,000; 15,000; 20,000; 30,000; 40,000; 50,000; 60,000; 70,000; 80,000; 90,000; 100,000 or more bases or base pairs. In some aspects of the disclosure, the difference in mean molecular sequencing size between two or more subsets of nucleic acid molecules is at least about 200 bases or bases pairs. Alternatively, the difference in mean molecular sequencing size between two or more subsets of nucleic acid molecules is at least about 300 bases or bases pairs.

[0186] Two or more subsets of nucleic acid molecules may be at least partially complementary. For example, a first subset of nucleic acid molecules may comprise nucleic acid molecules comprising at least a first portion of the genome and a second subset of nucleic acid molecules may comprise nucleic acid molecules comprising at least a second portion of the genome, wherein the first and second portion of the genome differ by one or more nucleic acid molecules. Thus, the first subset and the second subset are at least partially complementary. The complementarity of two or more subsets of nucleic acid molecules may be at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, or more. As used herein, the term "complementarity of two or more subsets of nucleic acid molecules" generally refers to genomic content of the two or more subsets and the extent to which the two or more subsets encompass the content of one or more genomic regions. For example, a first subset of nucleic acid molecules comprises 50% of total high GC exomes and a second subset of nucleic acid molecules comprises 50% of the total low GC exomes, then the complementarity of the two subsets of nucleic acid molecules in reference to an entire exome is 50%. In another example, a first subset of nucleic acid molecules comprises 100% of the total bead bound nucleic acid molecules and the second subset of nucleic acid molecules comprises 100% of the total bead free nucleic acid molecules, the complementarity of the two subsets in reference to the total nucleic acid molecules is 100%.

[0187] Subsets of nucleic acid molecules may comprise bead bound nucleic acid molecules. Two or more subsets of nucleic acid molecules may be differentiated into bead bound nucleic acid molecules

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and bead free nucleic acid molecules. For example, a first subset of nucleic acid molecules may comprise one or more bead bound nucleic acid molecules and a second subset of nucleic acid molecules may comprise bead free nucleic acid molecules. Bead free nucleic acid molecules may refer to nucleic acid molecules that are not bound to one or more beads. Bead free nucleic acid molecules may refer to nucleic acid molecules that have been eluted from one or more beads. For example, the nucleic acid molecule from a bead bound nucleic acid molecule may be eluted to produce a bead free nucleic acid molecule.

[0188] Subsets of nucleic acid molecules may comprise capture probe hybridized nucleic acid molecules. Two or more subsets of nucleic acid molecules may be differentiated into capture probe hybridized nucleic acid molecules and capture probe free nucleic acid molecules. For example, a first subset of nucleic acid molecules may comprise one or more capture probe hybridized nucleic acid molecules and a second subset of nucleic acid molecules may comprise capture probe free nucleic acid molecules. Capture probe free nucleic acid molecules may refer to nucleic acid molecules that are not hybridized to one or more capture probes. Capture probe free nucleic acid molecules may refer to nucleic acid molecules that are dehybridized from one or more capture probes. For example, the capture probe from a capture probe hybridized nucleic acid molecule may be removed to produce a capture probe free nucleic acid molecule.

[0189] Capture probes may hybridize to one or more nucleic acid molecules in a sample or in a subset of nucleic acid molecules. Capture probes may hybridize to one or more genomic regions. Capture probes may hybridize to one or more genomic regions within, around, near, or spanning one or more genes, exons, introns, UTRs, or a combination thereof. Capture probes may hybridize to one or more genomic regions spanning one or more genes, exons, introns, UTRs, or a combination thereof. Capture probes may hybridize to one or more known inDels. Capture probes may hybridize to one or more known structural variants.

[0190] Subsets of nucleic acid molecules may comprise labeled nucleic acid molecules. Two or more subsets of nucleic acid molecules may be differentiated into labeled nucleic acid molecules and non-labeled nucleic acid molecules. For example, a first subset of nucleic acid molecules may comprise one or more labeled nucleic acid molecules and a second subset of nucleic acid molecules may comprise non-labeled nucleic acid molecules. Non-labeled nucleic acid molecules may refer to nucleic acid molecules that are not attached to one or more labels. Non-labeled nucleic acid molecules may refer to

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nucleic acid molecules that have been detached from one or more labels. For example, the label from a labeled nucleic acid molecule may be removed to produce a non-labeled nucleic acid molecule.

[0191] The methods as disclosed herein may comprise, or comprise the use of, one or more labels. The one or more labels may be attached to one or more capture probes, nucleic acid molecules, beads, primers, or a combination thereof. Examples of labels include, but are not limited to, detectable labels, such as radioisotopes, fluorophores, chemiluminophores, chromophore, lumiphore, enzymes, colloidal particles, and fluorescent microparticles, quantum dots, as well as antigens, antibodies, haptens, avidin/streptavidin, biotin, haptens, enzymes cofactors/substrates, one or more members of a quenching system, a chromogens, haptens, a magnetic particles, materials exhibiting nonlinear optics, semiconductor nanocrystals, metal nanoparticles, enzymes, aptamers, and one or more members of a binding pair.

[0192] The one or more subsets of nucleic acid molecules may be subjected to one or more assays. The one or more subsets of nucleic acid molecules may be subjected to one or more assays based on their biochemical features. The one or more subsets of nucleic acid molecules may be subjected to one or more assays based on their genomic region features. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more assays. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more assays based on their biochemical features. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more assays based on their genomic region features. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more identical assays. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more identical assays based on their biochemical features. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more identical assays based on their genomic region features. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more similar assays. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more similar assays based on their biochemical features. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more similar assays based on their genomic region features. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more different assays. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more different assays based on their biochemical features. The one or more subsets of nucleic acid molecules may be subjected to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or

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more different assays based on their genomic region features. The two or more subsets of nucleic acid molecules may be subjected to one or more identical processing operations based on their biochemical features. The two or more subsets of nucleic acid molecules may be subjected to one or more identical processing operations based on their genomic region features. The two or more subsets of nucleic acid molecules may be subjected to one or more similar processing operations based on their biochemical features. The two or more subsets of nucleic acid molecules may be subjected to one or more similar processing operations based on their genomic region features. The two or more subsets of nucleic acid molecules may be subjected to one or more different processing operations based on their biochemical features. The two or more subsets of nucleic acid molecules may be subjected to one or more different processing operations based on their genomic region features.

[0193] The methods as disclosed herein may comprise, or comprise the use of, producing two or more subsets of nucleic acid molecules. The two or more subsets of nucleic acid molecules may be separated fluidically, separated into two or more containers, separated into two or more locations, or a combination thereof. For example, a first subset of nucleic acid molecules and a second subset of nucleic acid molecules are fluidically separated. In another example, a first subset of nucleic acid molecules is in a first container and a second subset of nucleic acid molecules is in a second container. In yet another example, a first subset of nucleic acid molecules and a second subset of nucleic acid molecules are assigned to two or more locations on a first container, and a third subset of nucleic acid molecules is in a second container.

[0194] As used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" can include one or a plurality of such cells, and reference to "the peptide" can include reference to one or more peptides and equivalents thereof, e.g., polypeptides, and so forth.

[0195] Where a range of values is provided, it is understood that each intervening value between the upper and lower limits of that range, to the tenth of the unit of the lower limit, unless the context clearly dictates otherwise, is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range, and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically

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excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

EXAMPLES

[0196] The following examples are given for the purpose of illustrating various embodiments of the present disclosure and are not meant to limit the present disclosure. The present examples, along with the methods described herein, are exemplary and are not intended as limitations on the scope of the present disclosure.

Example 1. Generation of a developmental mutation map.

[0197] The following illustrates an example of generating a developmental mutation map utilizing the methods disclosed herein. A developmental tree, for example of the kind depicted in **FIG. 1**, is used to map differential mutations to various tissues. The developmental tree depicts a developmental relationship between the tissues of an organism. To generate the developmental mutation map, various tissue samples are obtained from an individual. These samples are obtained from all over the individual's body and can include samples from blood, a skin biopsy, a hair sample, and the like. Nucleic acids are extracted from the samples and are sequenced by whole genome sequencing (WGS) to identify differential mutations between the various tissue samples. At some time in the future, the individual undergoes a procedure (e.g., a colonoscopy). A biopsy of the tissue (e.g., a biopsy of the colon) is taken during the procedure, nucleic acids are extracted from the biopsy, and the nucleic acids are sequenced to identify additional differential mutations. The differential mutations are mapped onto the developmental tree by associating the tissue source on the tree to the differential mutation. For example, a mutation is identified in the sample obtained from the pancreas, but not in lungs. This suggests that the mutation occurred sometime during branching of the primitive gut to the lungs and the digestive tube. All of the identified mutations are mapped in this fashion generating a comprehensive developmental mutation map.

Example 2. Diagnosis of pancreatic cancer in a patient by sampling nucleic acids distal to their origin.

[0198] The following illustrates an example of identifying the origin of a distal nucleic acid utilizing the methods disclosed herein. A blood sample is obtained from a patient during a routine visit to the clinic. Cell-free DNA (cfDNA) is extracted from the blood sample and is sequenced. Sequence reads are aligned to a reference sequence and mosaic variants are identified. A mutation is identified that is

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represented more frequently in the cfDNA than may be expected under ordinary conditions. The mutation is mapped to a developmental mutation map that was previously generated for the patient using the methods of Example 1. The mutation is identified as a mutation that was previously determined to be associated with the pancreas. This mutation, as depicted on the developmental mutation map, is previously identified in the pancreas and the stomach, but not in the intestine or the bile duct, suggesting the mutation occurred after division of the primitive gut to the foregut, the midgut and the hindgut. This information suggests that a tissue of the foregut may be under stress. A biopsy of the pancreas and the stomach are taken. The sample from the stomach is negative but the sample from the pancreas indicates the presence of a small tumor. The patient is diagnosed with pancreatic cancer far earlier than may otherwise be detected.

Example 3. Identification of the tissue of origin of a tumor metastasis.

[0199] The following illustrates an example of identifying the tissue of origin of a tumor metastasis. A metastatic tumor is distal to its origin. In some cancer cases, a primary tumor may no longer exist (e.g., if it has been destroyed by the immune system), but metastases may still exist in other places in the body. Because the cells of such a metastasis are derived from the primary tumor, which was itself derived from a cell of the tissue of origin, the metastatic cells may still carry the mosaic variants of the original tissue. This may be important because the treatment for a metastatic tumor can depend on the tissue of origin. In this example, a biopsy of a metastatic tumor is taken from a subject. The nucleic acid molecules are extracted from the tumor, sequenced and mosaic variants are identified. The mosaic variants are mapped to a developmental mutation map of the subject. In this example, a variant is identified in the metastatic tumor that maps to the pancreas on the mutation map. It is determined that the origin of the tumor is the pancreas. The subject is treated with an anti-cancer agent that is commonly used to treat pancreatic cancer (e.g., gemcitabine).

Example 4. Detecting variants in leukemia by tumor versus normal analysis.

[0200] In this example, a tumor versus normal analysis using the methods described herein is illustrated. In this example, the tumor is a leukemia and may be detected from a nucleic acid sample taken from a leukocyte. A blood sample is taken from a patient during a routine visit to the clinic. The blood sample is centrifuged to separate the blood into plasma, buffy coat, and red blood cells. The plasma contains cfDNA and the buffy coat contains leukocytes (i.e., some of which may be leukemia cells). Nucleic acids are extracted from both the plasma and the leukocytes, the nucleic acids are sequenced, and variants are detected in the samples. In this example, the sequence identified in the cfDNA is the

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"normal" sample and the leukocytes are the "tumor" sample. The sequences are compared and variants that occur only in the leukemia are identified.

[0201] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is 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 embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. 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. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

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CLAIMS

WHAT IS CLAIMED IS:

1. A method for detecting differential mutations in a blood sample of a subject, comprising:
   (a) separating said blood sample into at least a first component that includes cell-free or surface-bound nucleic acid molecules and a second component that includes leukocytes;
   (b) extracting nucleic acid molecules from said first and second components;
   (c) independently sequencing extracted nucleic acid molecules from said first and second components; and
   (d) comparing with a programmed computer processor nucleic acid sequences of said nucleic acid molecules of said first and second components to identify differential mutations.
2. The method of claim 1, further comprising (e) identifying a source of said cell-free or surface-bound nucleic acid molecules based on said differential mutations.
3. The method of claim 2, further comprising providing a report and/or a therapeutic intervention based on an identification of said source.
4. The method of claim 2, wherein said source is identified as a tissue or group of tissues of said subject.
5. The method of claim 2, further comprising comparing said differential mutation(s) to a mutation map of said subject to identify said source.
6. The method of claim 5, wherein said mutation map is a developmental mutation map or a spatial mutation map.
7. The method of claim 1, wherein (d) further comprises identifying variants in nucleic acid molecules of said first component with respect to nucleic acid molecules of said second component.
8. The method of claim 1, wherein said nucleic acid molecules of said second component are extracted by disrupting said leukocytes.
9. The method of claim 1, wherein said nucleic acid molecules extracted from said first and second components are sequenced in a combined pool.

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ABSTRACT OF THE DISCLOSURE

Disclosed herein are methods for improving detection and monitoring of human diseases. The methods can be used to provide spatial and/or developmental localization of the source of each differential mutation within the body. The methods can also be used to generate a mutation map of a subject. And the mutation map can be used to monitoring state(s) of health of one or more tissues of a subject.

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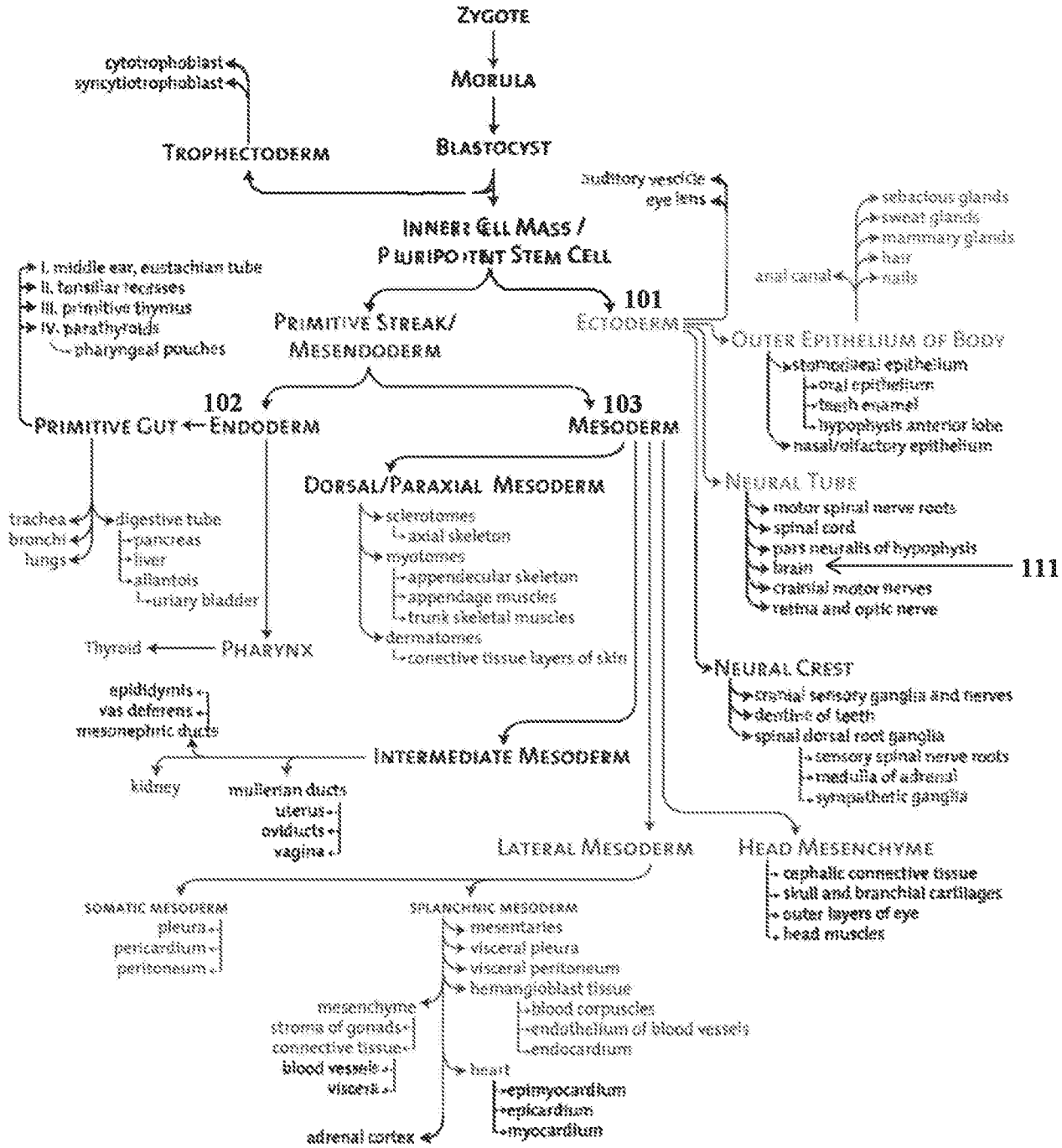

Zygote
Morula
Blastocyst
cytotrophoblast
syncytiotrophoblast
Trophectoderm
Inner Cell Mass / Pluripotent Stem Cell
auditory vesicle
eye lens
sebacious glands
sweat glands
mammary glands
hair
nails
anal canal
I. middle ear, eustachian tube
II. tonsillar recesses
III. primitive thymus
IV. parathyroids
pharyngeal pouches
Primitive Streak/ Mesendoderm
101
Ectoderm
Outer Epithelium of Body
stomodeal epithelium
oral epithelium
teeth enamel
hypophysis anterior lobe
nasal/olfactory epithelium
102
Endoderm
Primitive Gut
103
Mesoderm
Neural Tube
motor spinal nerve roots
spinal cord
pars neuralis of hypophysis
brain
111
cranial motor nerves
retina and optic nerve
trachea
bronchi
lungs
digestive tube
pancreas
liver
allantois
urinary bladder
Dorsal/Paraxial Mesoderm
sclerotomes
axial skeleton
myotomes
appendicular skeleton
appendage muscles
trunk skeletal muscles
dermatomes
connective tissue layers of skin
Thyroid
Pharynx
Neural Crest
cranial sensory ganglia and nerves
dentine of teeth
spinal dorsal root ganglia
sensory spinal nerve roots
medulla of adrenal
sympathetic ganglia
epididymis
vas deferens
mesonephric ducts
Intermediate Mesoderm
kidney
mullerian ducts
uterus
oviducts
vagina
Lateral Mesoderm
Head Mesenchyme
cephalic connective tissue
skull and branchial cartilages
outer layers of eye
head muscles
somatic mesoderm
pleura
pericardium
peritoneum
splanchnic mesoderm
mesentaries
visceral pleura
visceral peritoneum
hemangioblast tissue
blood corpuscles
endothelium of blood vessels
endocardium
mesenchyme
stroma of gonads
connective tissue
blood vessels
viscera
heart
epimyocardium
epicardium
myocardium
adrenal cortex

FIG. 1

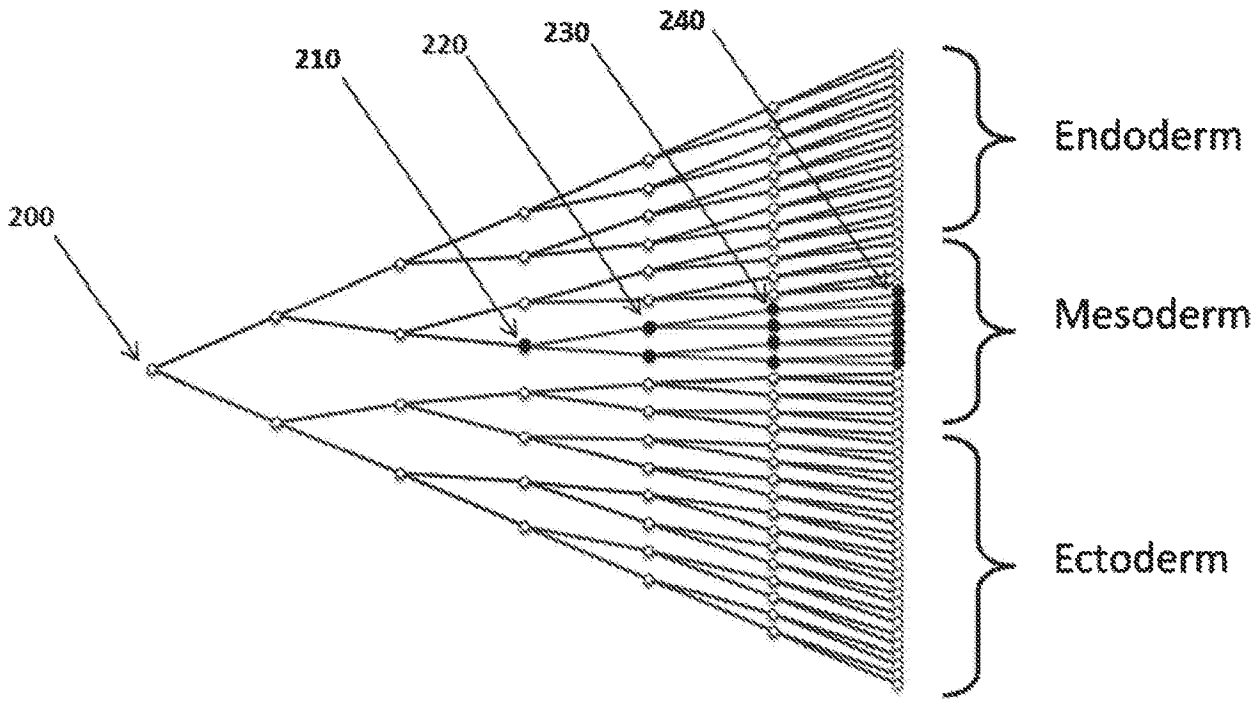


FIG. 2

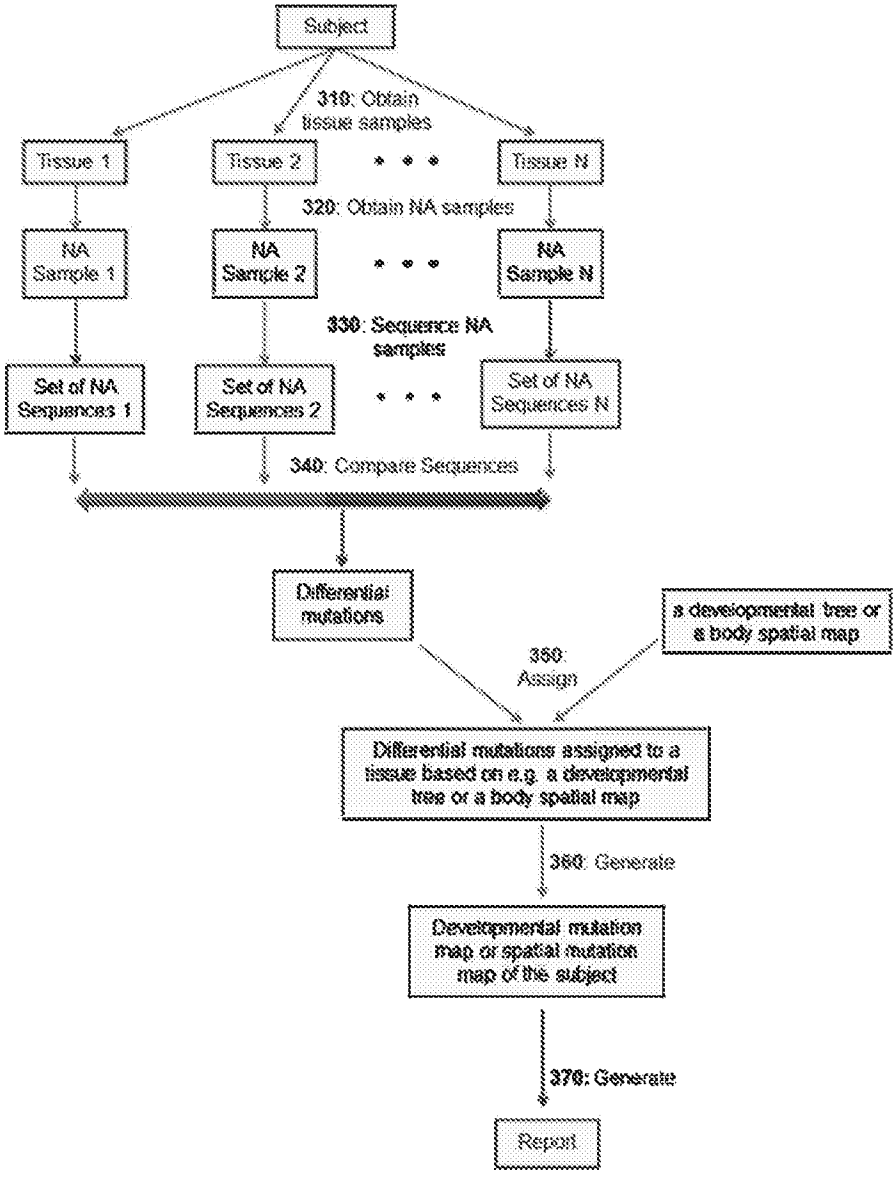

Subject
310: Obtain tissue samples
Tissue 1
Tissue 2
Tissue N
320: Obtain NA samples
NA Sample 1
NA Sample 2
NA Sample N
330: Sequence NA samples
Set of NA Sequences 1
Set of NA Sequences 2
Set of NA Sequences N
340: Compare Sequences
Differential mutations
a developmental tree or a body spatial map
350: Assign
Differential mutations assigned to a tissue based on e.g. a developmental tree or a body spatial map
360: Generate
Developmental mutation map or spatial mutation map of the subject
370: Generate
Report

FIG. 3

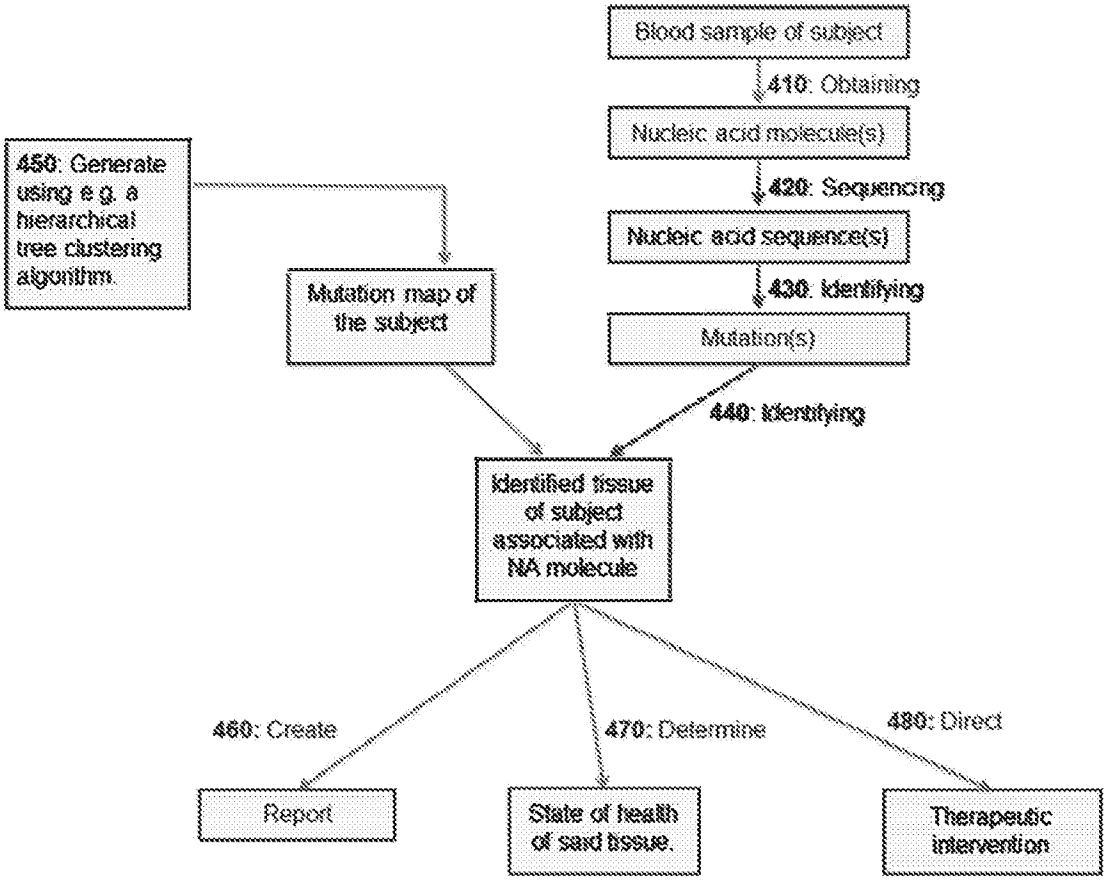

Blood sample of subject
410: Obtaining
Nucleic acid molecule(s)
420: Sequencing
Nucleic acid sequence(s)
430: Identifying
Mutation(s)
450: Generate using e.g. a hierarchical tree clustering algorithm
Mutation map of the subject
440: Identifying
Identified tissue of subject associated with NA molecule
460: Create
470: Determine
480: Direct
Report
State of health of said tissue.
Therapeutic intervention

FIG. 4

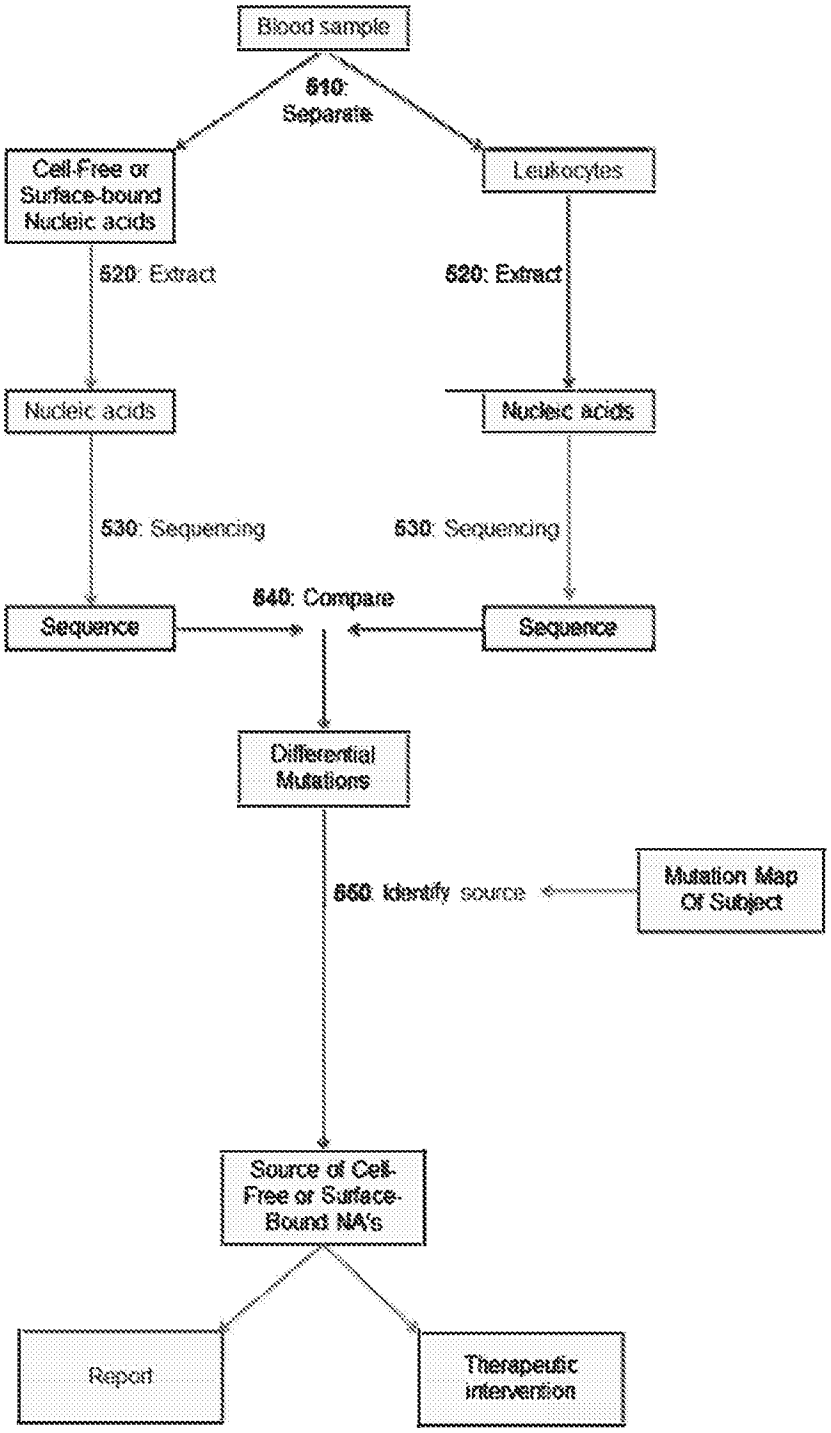

Blood sample
610: Separate
Cell-Free or Surface-bound Nucleic acids
Leukocytes
620: Extract
620: Extract
Nucleic acids
Nucleic acids
530: Sequencing
630: Sequencing
640: Compare
Sequence
Sequence
Differential Mutations
660: Identify source
Mutation Map Of Subject
Source of Cell-Free or Surface-Bound NA's
Report
Therapeutic intervention

FIG. 5

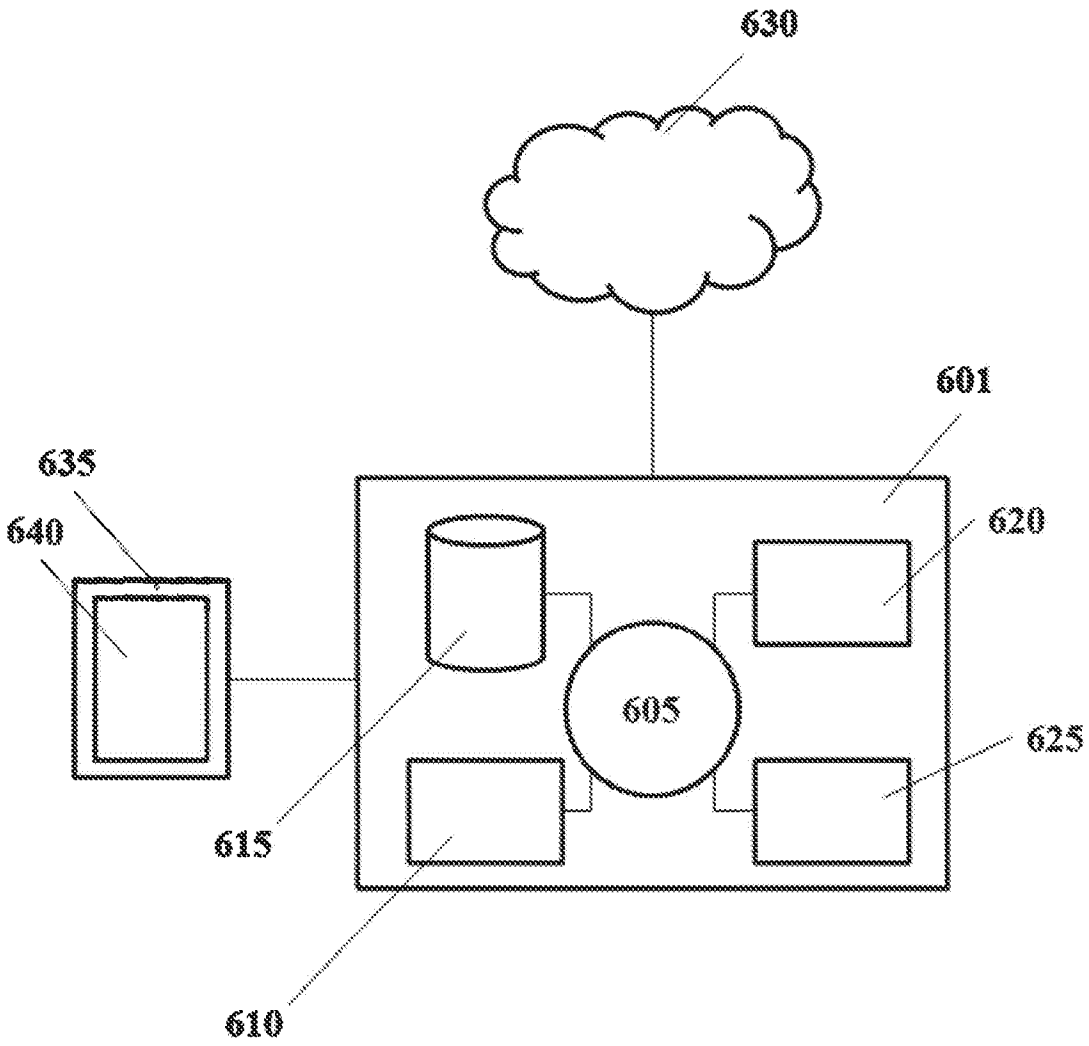


FIG. 6