

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): AmirAli TALASAZ

Serial Number: 16/277,724

Filing Date: February 15, 2019

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

Confirmation No.: 3144

Customer No.: 115823

Group Art Unit: 1637

Examiner: Not yet assigned

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

**RESPONSE TO NOTICE TO FILE MISSING PARTS AND
PRELIMINARY AMENDMENT**

Sir:

This reply is in response to the Notice to File Missing Parts of Nonprovisional Application mailed on March 7, 2019. The shortened statutory period for reply expires May 7, 2019, therefore, this response is timely filed. Applicant respectfully requests consideration of the above-referenced application in view of the following remarks:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The foregoing amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed. Applicant reserves the right to pursue the subject matter of the canceled claims in this or any other appropriate patent application.

Listing of Claims:

1. - 30. (Cancelled).

31. (New) A system of detecting somatic genetic variants of double-stranded cell-free deoxyribonucleic acid (cfDNA) in a blood sample for cancer testing in a human subject, comprising:

(a) a cfDNA sequencing sub-system to:

cause contact between 1 nanogram (ng) to 100 ng of cfDNA derived from the blood sample and a set of molecular barcodes comprising between 5 to 1,000 molecular barcodes to produce tagged parent polynucleotides, wherein at least 20% of the cfDNA are tagged with the set of molecular barcodes, and wherein a molecule of the cfDNA is joined to a molecular barcode at each end of the molecule of the cfDNA;

amplify a plurality of the tagged parent polynucleotides to produce progeny polynucleotides with associated molecular barcodes;

selectively enrich the progeny polynucleotides for target regions associated with cancer to generate enriched progeny polynucleotides; and

sequence at least a portion of the enriched progeny polynucleotides to produce sequencing reads; and

(b) a computer sub-system comprising a processor programmed to:

access the sequencing reads;

align the sequencing reads to a human reference genome to identify mapped sequencing reads, from among the sequencing reads, that map to the human reference genome;

identify beginning base positions in the human reference genome and end base positions in the human reference genome at which the mapped sequencing reads map to the human reference genome;

associate a first set of the mapped sequencing reads with a first cfDNA molecule in the blood sample based on one or more first molecular barcodes of the molecular barcodes, one or more first beginning base positions of the beginning base positions, and one or more first end base positions of the end base positions;

associate a second set of the mapped sequencing reads with a second cfDNA molecule in the blood sample based on one or more second molecular barcodes of the molecular barcodes, one or more second beginning base positions of the beginning base positions, and one or more second end base positions of the end base positions; and

detect, from among the first and second sets of the sequencing reads, the presence or absence of one or more somatic genetic variants comprising a single nucleotide variant (SNV), a copy number variation (CNV), an insertion or deletion (indel), and gene fusion.

32. (New) The system of claim 31, wherein the cfDNA sequencing sub-system comprises a nucleic acid sequencer.
33. (New) The system of claim 32, wherein the nucleic acid sequencer is to perform sequencing-by-synthesis on the at least a plurality of enriched progeny polynucleotides to produce the sequencing reads.
34. (New) The system of claim 32, wherein the nucleic acid sequencer is to perform pyrosequencing, single-molecule sequencing, nanopore sequencing, semiconductor sequencing, sequencing-by-ligation or sequencing-by-hybridization on the at least a plurality of enriched progeny polynucleotides to produce the sequencing reads.
35. (New) The system of claim 32, wherein the nucleic acid sequencer is to use a clonal single molecule array derived from the at least a plurality of enriched progeny polynucleotides to produce the sequencing reads.
36. (New) The system of claim 32, wherein the nucleic acid sequencer comprises a chip having an array of microwells for sequencing a sequencing library to produce the sequencing reads.
37. (New) The system of claim 31, wherein the computer sub-system comprises a memory, a hard drive or a computer server.

38. (New) The system of claim 31, wherein the computer sub-system comprises a communication interface to communicate with one or more other systems via a communication network.
39. (New) The system of claim 38, wherein the communication network comprises a telecommunication network, an internet, an extranet, or an intranet.
40. (New) The system of claim 38, wherein the communication network includes one or more computer servers capable of distributed computing.
41. (New) The system of claim 40, wherein distributed computing is cloud computing.
42. (New) The system of claim 32, wherein the processor is remotely located from the nucleic acid sequencer.
43. (New) The system of claim 42, wherein the processor is to generate a user interface comprising a result of the detection.
44. (New) The system of claim 43, wherein the processor is to provide the user interface via an electronic display in communication with the computer sub-system via a communication network.
45. (New) The system of claim 44, wherein the user interface comprises a graphical user interface (GUI) or a web-based user interface.
46. (New) The system of claim 44, wherein the electronic display is in a personal computer.
47. (New) The system of claim 44, wherein the electronic display is in an internet enabled computer.
48. (New) The system of claim 47, wherein the internet enabled computer is located at a location remote from the computer.
49. (New) The system of claim 31, wherein the cfDNA sequencing sub-system is to cause contact between 10 ng to 100 ng of cfDNA and the set of molecular barcodes to produce the tagged parent polynucleotides.
50. (New) The system of claim 31, wherein at least 30% of the cfDNA are tagged.
51. (New) The system of claim 31, wherein at least 40% of the cfDNA are tagged.
52. (New) The system of claim 31, wherein at least 50% of the cfDNA are tagged.
53. (New) The system of claim 31, wherein an expected size distribution of the cfDNA comprises 140-180 nucleotides.

54. (New) The system of claim 31, wherein the cfDNA comprises circulating tumor DNA (ctDNA).
55. (New) The system of claim 31, wherein the set of molecular barcodes comprises between 5 to 100 molecular barcodes.
56. (New) The system of claim 55, wherein the molecular barcodes are at least 5 nucleotides in length.
57. (New) The system of claim 31, wherein the cfDNA sequencing sub-system comprises a device to perform polymerase chain reaction (PCR) to amplify the plurality of the tagged parent polynucleotides.
58. (New) The system of claim 31, wherein the processor is further programmed to generate a base call at each genetic locus of a plurality of genetic loci in the human reference genome for the first and second sets of the mapped sequencing reads.
59. (New) The system of claim 58, wherein the processor is further programmed to measure a frequency of one or more bases called at the locus from among the first and second sets of the mapped sequencing reads.
60. (New) The system of claim 31, wherein the cfDNA sequencing sub-system is to implement next-generation sequencing, and wherein the cfDNA sequencing sub-system includes a device to perform PCR to amplify the plurality of the tagged parent polynucleotides.

REMARKS

Applicant received a Notice to File Missing Parts mailed March 7, 2019, indicating additional claim fees were due for pending claims 1-30. Applicant submitted a Preliminary Amendment on March 6, 2019 cancelling claims 4-30. Claims 1-3 remained pending. As such, the requirement for additional claim fees of the Notice to File Missing Parts is moot.

Applicant hereby submits a subsequent Preliminary Amendment. After entry of the above-referenced claim amendments, claims 1-3 are cancelled and claims 31-60 are newly added. Support for these new claims may be found throughout the application as filed, for example, at least at paragraphs [0044], [0098], [00249]-[00252], [00322]-[00331] and Figure 15.

With the cancellation of claims 1-30 and the addition of claims 31-60, no further claim fees are due are believed to be due. However, the Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 60-2231(Attorney Docket No. 42534-704.310).

A copy of the Notice to File Missing Parts is also submitted herewith.

CONCLUSION

Should any questions arise, the USPTO staff member is encouraged to contact the undersigned patent practitioner.

Respectfully submitted,
GUARDANT HEALTH, INC.

Date: May 7, 2019

By: /Timothy A. Hott/

Timothy A. Hott
Registration No.: 67740

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



UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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NOTICE OF ALLOWANCE AND FEE(S) DUE

115823 7590 06/04/2020
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

Table with 2 columns: EXAMINER (PRIEST, AARON A), ART UNIT (1637), PAPER NUMBER

DATE MAILED: 06/04/2020

Table with 5 columns: APPLICATION NO. (16/277,724), FILING DATE (02/15/2019), FIRST NAMED INVENTOR (AmirAli TALASAZ), ATTORNEY DOCKET NO. (GH0002US-CON11), CONFIRMATION NO. (3144)

TITLE OF INVENTION: SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION

Table with 7 columns: APPLN. TYPE (nonprovisional), ENTITY STATUS (UNDISCOUNTED), ISSUE FEE DUE (\$1000), PUBLICATION FEE DUE (\$0.00), PREV. PAID ISSUE FEE (\$0.00), TOTAL FEE(S) DUE (\$1000), DATE DUE (09/04/2020)

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

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

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies. If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above. If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)". For purposes of this notice, small entity fees are 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 and an extra copy of the form should be submitted. 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.

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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Alexandria, Virginia 22313-1450

By fax, send to: **(571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the **ISSUE FEE** and **PUBLICATION FEE** (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence 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)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

115823 7590 06/04/2020
Wilson Sonsini Goodrich & Rosati / Guardant Health
650 Page Mill Road
Palo Alto, CA 94304

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.
16/277.724	02/15/2019	AmirAli TALASAZ	GH0002US-CON11	3144

TITLE OF INVENTION: **SYSTEMS AND METHODS TO DETECT RARE MUTATIONS AND COPY NUMBER VARIATION**

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	09/04/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
PRIEST, AARON A	1637	702-190000

<p>1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).</p> <p><input type="checkbox"/> Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.</p> <p><input type="checkbox"/> "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. Use of a Customer Number is required.</p>	<p>2. For printing on the patent front page, list</p> <p>(1) The names of up to 3 registered patent attorneys or agents OR, alternatively, _____ 1</p> <p>(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. _____ 2</p> <p>_____ 3</p>
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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. _____



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Table with columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO., EXAMINER, ART UNIT, PAPER NUMBER. Includes application details for AmirAli TALASAZ and examiner Aaron A. Priest.

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.

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. 16/277,724	Applicant(s) TALASAZ, AmirAli	
Examiner Aaron Priest	Art Unit 1637	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 5/7/2019.
 A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2. An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 3. The allowed claim(s) is/are See Continuation Sheet. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov**.
- 4. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
Certified copies:
 - a) All b) Some *c) None of the:
 - 1. Certified copies of the priority documents have been received.
 - 2. Certified copies of the priority documents have been received in Application No. _____.
 - 3. Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

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

- 5. CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
- 6. DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- 1. Notice of References Cited (PTO-892)
- 2. Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date See Continuation Sheet.
- 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 _____.

/AARON A PRIEST/
Primary Examiner, Art Unit 1637

Continuation of 3. The allowed claim(s) is/are: 31,33-48,54-56,58-59 and 61-62

Continuation of Attachment(s) 2. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 5/17/2019 (x6), 6/5/2019,7/1/2019,8/2/2019,8/22/2019,11/6/2019,3/17/2020,4/8/2020,5/11/2020

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.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Jackie Stroncek on 05/05/2020.

Please amend the claims as follows (see underlining, ~~striketrough~~, "(canceled)" and "(new)"):

31. (Currently Amended) A system ~~of detecting~~configured to detect somatic genetic variants ~~of double-stranded~~in cell-free deoxyribonucleic acid (cfDNA) in a blood sample for cancer testing in a human subject, comprising:

- (a) ~~cfDNA~~a nucleic acid sequencer for sequencing sub-system to:
~~cause contact between 1 nanogram (ng) to 100 ng of cfDNA derived from the blood sample and a set of molecular barcodes comprising between 5 to 1,000 molecular barcodes to produce tagged parent~~a plurality of polynucleotides, wherein at least 20% of the cfDNA are tagged with the derived from non-uniquely tagged cfDNA to produce a set of sequencing reads, wherein the non-uniquely tagged cfDNA comprises molecular barcodes from a set of molecular barcodes, and wherein joined at both ends of a molecule of the cfDNA, and wherein the cfDNA is joined that map to a molecular barcode at each endmappable base position of the different molecular barcodes ranging from at least 2 and fewer than a number of cfDNA molecules that map to the mappable base position;

~~amplify a plurality of the tagged parent polynucleotides to produce progeny polynucleotides with associated molecular barcodes; selectively enrich the progeny polynucleotides for target regions associated with cancer to generate enriched progeny polynucleotides; and~~

~~sequence at least a portion of the enriched progeny polynucleotides to produce sequencing reads; and~~

(b) a computer ~~sub-system~~ comprising a processor programmed to:

~~access the sequencing reads;~~

access sequencing reads from the set of sequencing reads, wherein the sequencing reads comprise nucleic acid sequences corresponding to (1) a cfDNA molecule from among the non-uniquely tagged cfDNA and (2) nucleic acid sequences of the molecular barcodes associated with the cfDNA molecule;

align the sequencing reads to ~~a~~the human reference genome to identify mapped sequencing reads, from among the sequencing reads, that map to the human reference genome;

identify beginning base positions in the human reference genome and end base positions in the human reference genome at which the mapped sequencing reads map to the human reference genome;

associate a first set of the mapped sequencing reads with a first cfDNA molecule in the blood sample based on ~~one or more first molecular barcodes~~barcode sequences of the molecular barcodes, ~~one or more~~associated with the first cfDNA molecule, a first beginning base positions of the beginning base positions, and ~~one or more~~a first end base positions of the end base positions;

associate a second set of the mapped sequencing reads with a second cfDNA molecule in the blood sample based on ~~one or more second~~the molecular barcodes sequences of the molecular barcodes, ~~one or more~~associated with the second cfDNA molecule, a second beginning base

positions of the beginning base positions, and ~~one or more~~ a second end base positions of the end base positions; ~~and~~

detect, from among at least the first and second sets of the mapped sequencing reads, the presence or absence of one or more somatic genetic variants comprising a single nucleotide variant (SNV), a copy number variation (CNV), an insertion or deletion (indel), and gene fusion.

32. (Canceled)
33. (Currently Amended) The system of claim ~~32~~31, wherein the nucleic acid sequencer is to perform sequencing-by-synthesis ~~on the at least a plurality of enriched progeny polynucleotides~~ to produce the set of sequencing reads.
34. (Currently Amended) The system of claim ~~32~~31, wherein the nucleic acid sequencer is to perform pyrosequencing, single-molecule sequencing, nanopore sequencing, semiconductor sequencing, sequencing-by-ligation or sequencing-by-hybridization ~~on the at least a plurality of enriched progeny polynucleotides~~ to produce the set of sequencing reads.
35. (Currently Amended) The system of claim ~~32~~31, wherein the nucleic acid sequencer is to use a clonal single molecule array ~~derived from the at least a plurality of enriched progeny polynucleotides~~ to produce the set of sequencing reads.
36. (Currently Amended) The system of claim ~~32~~31, wherein the nucleic acid sequencer comprises a chip having an array of microwells ~~for sequencing a sequencing library~~ to produce the set of sequencing reads.
37. (Currently Amended) The system of claim 31, wherein the computer ~~sub-system~~ comprises a memory, a hard drive or a computer server.
38. (Currently Amended) The system of claim 31, wherein the computer ~~sub-system~~ comprises a communication interface to communicate with one or more other systems via a communication network.
41. (Currently Amended) The system of claim 40, wherein the distributed computing is cloud computing.

42. (Currently Amended) The system of claim ~~32~~31, wherein the processor is remotely located from the nucleic acid sequencer.

44. (Currently Amended) The system of claim 43, wherein the processor is to provide the user interface via an electronic display in communication with the computer ~~sub-system~~ via a communication network.

49–53. (Canceled)

55. (Currently Amended) The system of claim 31, wherein the set of molecular barcodes comprises molecular barcodes having between 5 to 100 different molecular barcode[[s]] sequences.

57. (Canceled)

60. (Canceled)

61. (New) The system of claim 31, wherein the set of molecular barcodes comprises molecular barcodes having between 2 to 1,000,000 different molecular barcode sequences.

62. (New) The system of claim 31, wherein the processor is further programmed to determine if the first or second sets align to one or more predefined regions of the human reference genome.

Reasons for Allowance

Claims 31, 33-48, 54-56, 58-59 and 61-62 are allowed because the prior art fails to teach or suggest sequencing and processing *cfDNA* that was *non-uniquely* tagged and using the non-unique tags and the beginning base and the end base to associate sequence reads. In other words, the barcoding yields *non-unique barcodes* because the amount of *cfDNA* (and number of different *cfDNA* molecules) is in excess of the number of barcodes (Spec., para. 0252 (“non-uniquely tagged, that is, the number of different identifiers can be at least at least 2 and fewer than the number of polynucleotides that map to the mappable base position”)). Contrary to this, the closest prior art teaches to use an *excess* of barcode adapters to DNA (and number of different

DNA molecules) to *uniquely* barcode. See Schmitt *et al.*, *Detection of ultra-rare mutations by next-generation sequencing*, Proc Natl Acad Sci U S A. 2012 Sep 4;109(36):14508-13. Epub 2012 Aug 1; US 9,752,188; WO 2012/042374 A2; Kinde *et al.*, *Detection and quantification of rare mutations with massively parallel sequencing*, PNAS June 7, 2011 108 (23) 9530-9535. Furthermore, a number of the SALK patent documents (e.g. US 10,604,804) include some of the same authors as the Schmitt reference. These SALK patent documents teach the same invention as in Schmitt, but contain language arguably directed to circulating DNA and “non-unique” barcoding. For example, US 10,604,804 contains claims directed to “attaching tags comprising barcodes selected from a plurality of distinct barcode sequences to said *circulating nucleic acid molecules* obtained from said bodily sample of the subject” and “generat[ing] *non-uniquely tagged* parent polynucleotides.” As to “non-uniquely” barcoding, US 10,604,804 has a single sentence suggesting “[a] hybrid method using a combination of sheared ends and a shorter n-mer tag (such as 1 or 2 or 3 or 4 or more degenerate or semi-degenerate bases) in the adaptor may also serve as unique molecular identifiers.” At the least, this definition of “non-uniquely” barcoding is different from the current Application: “A set of polynucleotides in the composition that map to a mappable base position in a genome can be non-uniquely tagged, *that is, the number of different identifiers can be at least at least 2 and fewer than the number of polynucleotides that map to the mappable base position*” (para. 0252). Thus, at the least, US 10,604,804 does not “non-uniquely” barcode as defined by the instant application because neither Schmitt nor US 10,604,804 disclose the number of different identifiers can be at least at least 2 and fewer than the number of polynucleotides that

map to the mappable base position (e.g. 100-1000,000 haploid genome equivalents of cfDNA versus 2-1,000 different molecular barcode sequences of at least 5 nucleotides in length, as claimed).

As to cfDNA, the background section of the Specification of US 10,604,804 indicates that deep sequencing has been implemented for “nucleic acid-based serum biomarkers.” US 10,604,804 never explicitly states that their method can be used with circulating/cell-free nucleic acids. Most likely this is because it was not enabled to be used with cfDNA as explained in Perakis. Perakis *et al.*, *Advances in Circulating Tumor DNA Analysis*, *Adv Clin Chem.* 2017;80:73-153. Epub 2017 Jan 3, states that the “[a]lthough the same group [Schmitt/US 10,604,804 used this approach for selective enrichment of small genomic regions, the original protocol has not yet been used with ctDNA” and “[p]rospects of success are limited since the method is relatively inefficient when limited amounts of input DNA—as it is most likely the case for cfDNA—are used” (pg. 102). In other words, skilled artisans expected that the method of Schmitt/US 10,604,804 was not enabled for cfDNA.

Thus, the claims are allowed because the prior art fails to teach or suggest an enabled step (a) with cfDNA and (b) the “non-uniquely” barcoding is not disclosed in US 10,604,804.

As to subject matter eligibility under Section 101, even if the claims were directed to a judicial exception, yet the claims require to non-unique barcoding with non-routine cfDNA:barcode ratios to allow non-routine data processing of sequence reads that amounts to an inventive sequencing concept. Thus, the claims are patent eligible at a minimum for this reason.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 31, 33-48, 54-56, 58-59 and 61-62 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AARON PRIEST whose telephone number is (571) 270-1095. The examiner can normally be reached on Monday-Friday 10am-6pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free] If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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